# The efficacy of intermittent directly observed isoniazid in preventing tuberculosis in HIV-infected adults with advanced disease

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# PLAGIARISM DECLARATION

I, **Ashraf Allie Mohammed**, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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# PRIOR PUBLICATIONS

Some of the material used in this thesis has been previously published as indicated below:

Mohammed, A; Ehrlich, R; Wood, R; Cilliers, F & Maartens, G. (2004). Screening for tuberculosis in adults with advanced HIV infection prior to preventive therapy. *Int J Tuberc Lung Dis,* **8**: 792-795.

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# ABSTRACT


## Introduction

Meta-analysis of the treatment of latent tuberculosis infection (LTBI) in HIV-infected adults has shown significant reduction in the incidence of tuberculosis in participants with a positive tuberculin skin test (TST), but not in those with a negative TST. However, there are insufficient data on patients with advanced HIV disease from high tuberculosis incidence areas.

It is important to exclude tuberculosis prior to such preventive therapy, but this can be difficult in patients with symptomatic HIV disease. A tuberculosis screening instrument is thus needed to ensure that patients placed on preventive therapy do not have tuberculosis. Furthermore, to ensure adherence and avoid drug resistance optimal supervision of the treatment administrations is required.

## Methods

Patients with clinically advanced HIV disease were screened for active tuberculosis using a symptom questionnaire, measured weight loss, chest radiography, sputum microscopy and culture prior to receiving tuberculosis preventive therapy. Once tuberculosis was excluded, a randomized double-blind trial was conducted comparing INH with placebo among TST negative status participants with WHO Stage 3 or 4 HIV disease. INH/placebo was administered for 12 months by patient-nominated supervisors.

TST-positive participants were given open-label INH. Participants who did not have access to ART were followed up for 24 months with 6-monthly sputum culture and chest radiography. All those enrolled for the trial were required to visit a clinic on a monthly basis for 12 months during the period of weekly

intermittent supervised administration of INH/placebo to assess for tuberculosis and adherence.

**Results**

A total of 118 participants were enrolled: TST was negative in 98. Tuberculosis was diagnosed in 11 of 129 patients screened. A simple screening instrument of two or more of the symptoms cough, night sweats or fever, (plus measured weight loss) had a sensitivity of 100% and specificity of 88.1% (against the gold standard of sputum culture) and positive and negative predictive values of 44% and 100%, respectively. In the randomized trial arms, the incidence of tuberculosis was 18/100 person-years (py) in the INH arm and 11.6/100 py in the placebo arm [hazard ratio 1.59, 95% confidence interval (CI) 0.57-49)].

There was no significant difference in mortality, hospitalization rate or CD4+ lymphocyte decline. Patient adherence for INH/placebo was 85% and was significantly higher among participants with work-based treatment supervisors than among those who were supervised by home-based or community-based treatment supervisors.

The daily self-administered treatment (SAT) of cotrimoxazole (CTX) showed a good adherence especially among the TST positive participants, where a greater benefit in terms of survival among participants with good cotrimoxazole adherence was observed.

**Conclusion**

A simple screening instrument can effectively exclude tuberculosis in patients with advanced HIV disease, prior to isoniazid preventive therapy (IPT). Once tuberculosis has been excluded, TST can be done to assess eligibility for preventive therapy. No association between IPT and reduction of tuberculosis among the TST-negative adults with advanced HIV disease was

found. High levels of adherence were observed with patient nominated supervisors.

This study also shows that there was a greater benefit in terms of survival among participants with a threshold of ≥70% cotrimoxazole adherence. The mortality in the <70% cotrimoxazole adherence group was lower but not significant as the ≥70% cotrimoxazole adherence group (HR 1.28; 95% CI: 0.59 – 2.70). It was observed that the participants with a positive TST had significantly better cotrimoxazole adherence as compared to the participants with a negative TST.

A simple screening instrument had shown to effectively exclude tuberculosis in patients with advanced HIV disease. Hence, it is recommended that once tuberculosis has been excluded, TST can be done to assess eligibility for IPT. This should be included as component of active tuberculosis case finding integrated into HIV management at primary care and VCT. Because good adherence was attributed to patient nominated supervisors, it is recommended that in resource-limited settings it should also become an integral component of IPT.

Although no benefit was associated with IPT in participants with clinically advanced HIV and negative TSTs, (consistent with meta-analyses), access to antiretroviral therapy (ART) is increasing in resource-limited settings and hence there is a need for further investigation of the role of INH or other preventive therapy in patients receiving combination antiretroviral therapy.

# DEDICATION

I dedicate this thesis to all those participants who readily consented to participate in this clinical trial and whose hope and determination to live inspired me throughout this research. Their determination to overcome many of the insurmountable challenges they faced due to being afflicted by HIV/AIDS led me to reflect upon life from a different perspective. Their participation not only contributed immensely to this research but also added a completely new dimension to my life. I owe this incalculable debt to them.

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# ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse effects |
| **AIDS** | Acquired Immunodeficiency Syndrome |
| **ARV** | Anti-retroviral |
| **ART** | Anti-retroviral therapy |
| **ATS** | American Thoracic Society |
| **BCG** | Bacillus Calmette-Guérin |
| **B6** | Pyridoxine |
| **CBOs** | Community based organisations |
| **CDC** | Centers for Disease Control |
| **CI** | Confidence interval |
| **CTX** | Cotrimoxazole |
| **DOPTS** | Directly observed preventive therapy supervisor |
| **DOTS** | Directly observed therapy short course chemotherapy |
| **FBOs** | Faith based organisations |
| **GIS** | Geographical information system |
| **HAART** | Highly active anti-retroviral therapy |
| **HIV** | Human-immunodeficiency virus |
| **HX** | History (clinical) |
| **INH** | Isoniazid |
| **IPT** | Isoniazid preventive therapy |
| **IQR** | Inter-quartile range |
| **JTBCBTS** | Joint Tuberculosis Committee of British Thoracic Society |
| **KP** | Karnofsky Performance Scale Score |
| **LTBI** | Latent tuberculosis infection |
| **LTBT** | Latent tuberculosis treatment |
| **MDR** | Multi drug resistance |
| **MDR-TB** | Multi drug resistance tuberculosis |
| **MTb** | *Mycobacterium tuberculosis* |
| **MX** | Mantoux |
| **NGOs** | Non-governmental organisation |
| **NT** | No treatment |
| **NTM** | Non-tuberculous mycobacteria |

| | |
|---|---|
| **NPV** | Negative predictive value |
| **NTBCP** | National Tuberculosis Control Programme |
| **OIs** | Opportunistic Infections |
| **PPD** | Purified protein derivative |
| **PT** | Preventive therapy |
| **PPV** | Positive predictive value |
| **PTB** | Pulmonary tuberculosis |
| **PY** | Person years |
| **R** | Rifampicin |
| **RCT** | Randomized clinical trial |
| **RR** | Relative risk |
| **RX** | Treatment |
| **S** | Streptomycin |
| **SAT** | Self-administered treatment |
| **SLD** | Second-line drugs |
| **TB** | Tuberculosis |
| **TBCP** | Tuberculosis Control Programme |
| **TBPT** | Tuberculosis preventive therapy |
| **TST** | Tuberculin skin test |
| **UNAIDS** | Joint United Nations Programme on HIV/AIDS |
| **USAID** | United State Agency for International Development |
| **US** | Unites States |
| **VCT** | Voluntary counselling and testing |
| **WBC** | White blood count |
| **WHO** | World Health Organization |
| **WHO-MDG** | World Health Organization Millennium Development Goals |
| **XDR-TB** | Extensive drug resistant tuberculosis |
| **Z** | Pyrazinamide |
| **6H** | Six months of Isoniazid |
| **3H** | Three months of Isoniazid |
| **3HR** | Three months of Isoniazid plus Rifampicin |
| **2HR** | Two months of Isoniazid plus Rifampicin |
| **2RZ** | Two months of Rifampicin plus Pyrazinamide |

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# CHAPTER 1: INTRODUCTION

## 1.1 Tuberculosis: plague of the 21st century

### 1.1.1 Identification of *Mycobacterium tuberculosis*: 19th century milestone

Tuberculosis has been present in human settlements since time immemorial. To date there has been no conclusive evidence where and when Man first became afflicted with tuberculosis.

The isolation and identification of *Mycobacterium tuberculosis* (MTb) by Robert Koch in 1882 is still today regarded as a milestone for tuberculosis in the 19th century. This event became the catalyst for dramatic developments towards progress in the prevention, management and control of tuberculosis in that era. Today, in spite of these successes, tuberculosis returns to become one of the major killer infectious diseases of the 21st century.

Robert Koch aptly described tuberculosis morbidity and mortality: "*If the number of victims which a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infectious diseases, such as bubonic plague, Asiatic cholera, must rank far behind tuberculosis"* (Koch R, 1882). With the advent of the HIV/AIDS pandemic, this statement made more than 100 years ago remains valid to this day, despite the tremendous strides made in the treatment of tuberculosis in the 20th century.

### 1.1.2 Transmission of *Mycobacterium tuberculosis* (MTb)

The transmission of MTb, the causative agent for tuberculosis, occurs predominantly by means of airborne transmission. The risk of infection is largely dependent on the dose of droplet infection, duration of exposure and host susceptibility. This can take place when one is in contact with a sputum smear-positive individual with pulmonary tuberculosis (PTB). HIV-uninfected tuberculosis patients with undetected active or untreated PTB are infectious and can remain infectious or 1-2 years, infecting an average of 10 people per year (Styblo K, 1980). However, in poorly resourced countries this untreated case of pulmonary tuberculosis (PTB) could remain infectious for two years or more (Styblo K, 1980).

An infected person may remain latently infected (without being infectious) for life without developing active tuberculosis, if they are not subjected to the risk factors for active tuberculosis. Since HIV impairs the immune system, it has become the main risk factor for the development of tuberculosis. Other historical risk factors fuelling the tuberculosis epidemic include environmental factors (i.e. poverty, malnutrition, overcrowding), host factors (i.e. other diseases, tobacco use, substance abuse, silicosis/silica dust exposure, stress) and health service factors (i.e. quality of screening, diagnosis, adherence, latent tuberculosis Treatment (LTBT) for HIV positive patients).



### 1.1.3 Tuberculosis is a Global Public Health Emergency

On Friday April 23, 1993, the World Health Organisation (WHO) declared tuberculosis a global public health emergency (Editorial, CHASA, 1993). This heralded official acknowledgement of the worldwide resurgence of tuberculosis in the wake of the HIV pandemic, accompanied by an alarming increase in multi-drug resistant tuberculosis (MDR-TB); high mortality rates; lengthy and expensive treatment and poor rates of treatment success. The declaration by WHO that tuberculosis is a global

public health emergency aimed to support the global Tuberculosis Control Programme (TBCP), which had already recorded increased mortality rates in HIV/TB co-infected patients (WHO, 1992).

At least one-third (2 billion) of the world's population is estimated to be infected with tuberculosis (WHO 2003). In 2000, tuberculosis incidence rates were highest in the WHO African Region (290/100 000 per year; range: 265/100 000-331/100 000). In individuals between the ages of 15-49 years (in the WHO African Region), 31% of tuberculosis cases notified were attributable to HIV. Furthermore, an estimated 1.8 million ($5^{th}$ - $95^{th}$ percentiles, 1.6 - 2.2 million) deaths were because of tuberculosis among those aged 15-49 years, (Corbett EL *et al,* 2003). Of these deaths, 12% were attributed to HIV and tuberculosis was reported to be the cause of 11% of all adult AIDS deaths (Corbett EL *et al*, 2003).

Developing countries account for 95% of all cases of HIV infection and more than 99% of HIV-related deaths. It has been estimated that 95% of tuberculosis cases occur in developing countries resulting in 98% of tuberculosis-related deaths. The lifetime risk of active tuberculosis among HIV-infected adults is 50% as compared to 5-10% risk in adults without HIV infection (Pape JW, 2004). Furthermore, a study of HIV-infected adults attending HIV Clinics at the University of Cape Town between January 1986 and May 1996 reported an annual tuberculosis incidence exceeding 30% in patients with clinically advanced HIV disease from high tuberculosis burden communities. (Wood R *et al,* 2000).

In Africa, tuberculosis is thus the most common life-threatening opportunistic infection associated with HIV and the major cause of death among patients with acquired immunodeficiency syndrome (AIDS). The control of tuberculosis cannot be achieved without taking cognisance of

the negative impact of HIV/AIDS (Lee, JW & Kumaresan, JA, 2002) on the Tuberculosis Control Programme (TBCP).

### 1.1.4 The Need for New Strategies in Tuberculosis Control

Tuberculosis is preventable, treatable and curable; yet we have not been able to conquer this age-old disease. To date there is no reliable vaccine against tuberculosis. With the emergence of multi-drug resistant (MDR-TB) strains, our first line of defence, the six-month tuberculosis treatment regimen to cure patients with tuberculosis, is now threatened.

The emergence of *Mycobacterium tuberculosis* with extensive resistance to second line drugs is termed extensively drug resistant tuberculosis and termed as extensive drug resistant tuberculosis (XDR-TB). This too does not augur well for the global TBCP. Analysis of 17,690 tuberculosis isolates from 25 reference laboratories on 6 continents showed 20% multi-drug resistant (MDR) and 2% XDR-TB in a CDC-WHO survey conducted between 2000 and 2004 (MMWR, 2006). The recent outbreak of XDR-TB in Kwazulu Natal in South Africa, with alarmingly high mortality rates as was reported at the XVI International AIDS Conference in Toronto in August, 2006, (Gandhi NR *et al,* 2006), raised major public health concerns.



The WHO's Millennium Development Goals (WHO-MDG) for the global Tuberculosis Control Programme (TBCP) involve five principal targets. The first and second targets focus on the successful treatment of at least 85% of new smear positive cases and the detection of at least 70% of new smear positive cases by 2005. The third and fourth targets focus on attempts to at least halt and begin to reverse tuberculosis incidence by 2015; and halve tuberculosis prevalence between 1990 and 2015. The fifth target is focused on an attempt to halve the tuberculosis death rate between 1990 and 2015.

The TUBERCULOSIS burden in developing countries has overwhelmed the health services, especially in Sub-Saharan Africa where the vast majority of persons with HIV live (Corbett EL *et al,* 2003). The WHO global targets for tuberculosis control were postponed from 2000 to 2005 and evidence indicates that further postponement may be necessary as a result of the impact of the HIV pandemic (Harries AD *et al,* 2005). The advent of HIV has further exacerbated tuberculosis globally, particularly in vulnerable communities subjected to poverty and lack or absence of health resource settings and those whose immunity is reduced by HIV.

As in the case of other emerging and re-emerging diseases, there is now an urgent need to develop innovative strategies in the battle against tuberculosis in the 21st Century. In countries where HIV has contributed to a substantial increase in tuberculosis incidence, the focus should remain on tuberculosis Control Programmes where diagnosis and treatment of active tuberculosis cases should be a priority.

The use of directly observed treatment short course chemotherapy (DOTS) that could be incorporated into an intensive community-based programme that focuses focus on early diagnosis and treatment of HIV and AIDS-associated tuberculosis is but one of the strategies that could be implemented in resource poor settings (Narain JP & Lu YR, 2004; Maher D *et al,* 2005). A combination of highly active anti-retroviral treatment (HAART) in high HIV prevalence areas plus tuberculosis case finding curing tuberculosis would be effective in reducing tuberculosis incidence and deaths over the next 10 years. However, this would require high level of coverage and adherence to HAART (Currie CSM *et al,* 2003). Thus, the focus on reducing HIV incidence in preventing tuberculosis incidence and tuberculosis deaths is a long-term strategy (Currie CSM *et al,* 2003).

Thus, a four pronged strategy in reducing the incidence of tuberculosis would involve the 70% of tuberculosis detection rate and curing 85% of the tuberculosis active cases; reducing HIV incidence; initiating social upliftment programmes for socially vulnerable groups in the community and the prevention of tuberculosis by latent tuberculosis treatment (LTBT); (Mohammed, A, 2000).

In a cost effectiveness study (Bell JC *et al,* 1999) that was conducted among HIV-infected individuals in sub-Saharan Africa regarding preventive tuberculosis therapy, it was concluded that LTBT taken among TST positive HIV-infected in this region could extend life expectancy, reduce tuberculosis incidence and reduce health care and social costs. This study (Bell JC *et al,* 1999) recommends that tuberculosis control policy in sub-Saharan Africa should include preventive therapy.

The prevention of tuberculosis and tuberculosis deaths with Isoniazid Preventive Therapy (IPT) in HIV-infected patients from communities where tuberculosis is endemic has a modest effect and should be complemented with treatment of active tuberculosis cases and HAART (Currie CSM *et al,* 2003). However, to sustain effective tuberculosis control in the long term, latent tuberculosis treatment (LTBT) should be considered to complement the intensive strategy of treating active tuberculosis cases.



## 1.2 Co-infection (Tuberculosis and HIV)

### 1.2.1 Impact of tuberculosis and HIV co-Infection

There is a strong association between tuberculosis and HIV and the number of persons co-infected with tuberculosis and HIV is on the increase as the global prevalence of HIV increases. The prevalence of MTb and HIV coinfection is estimated to be 0.35% (11 million) with

coinfection prevalence rates of 5% or more in eight African countries (Corbett EL *et al,* 2003). And in South Africa it is estimated that the MTb/HIV coinfection to be 2 million in a population of 47 million.

The WHO report identifies 22 countries (all, except Russia, developing countries), including South Africa, that are considered to have 'high burden' tuberculosis infection rates. Every year it is estimated that 8 million people develop tuberculosis, of which 80% are notifications from these 22 'high burden' countries (WHO 2003). Almost 70% of tuberculosis -HIV co-infected people live in Sub-Saharan Africa, where HIV is the primary driving force behind the tuberculosis epidemic (Corbett EL *et al,* 2003). Tuberculosis, unlike other opportunistic infections, which occur in HIV/AIDS patients, is the only infectious disease that poses a public health threat to the community.

It has also been suggested that besides the increased susceptibility to tuberculosis subsequent to MTb infection, the increase of HIV-associated tuberculosis cases could increase MTb transmission rates at the community level and thus impacting on HIV-negative persons as well (Odiambo JA *et al,* 1999; Corbett EL *et al*, 2003)).

Furthermore, several countries have reported epidemic outbreaks of tuberculosis that had been associated with HIV with many of these reported outbreaks involved multi-resistant outbreaks of MTb strains (Agerton TB *et al,* 1999; Moss AR *et al*, 1997).

#### *1.2.1.1 Tuberculosis Morbidity and Mortality in HIV-infected Adults*

Tuberculosis is acknowledged as the major cause of morbidity and mortality in HIV-infected adults in sub-Saharan Africa (Nunn PP *et al,* 1994; Lucas SB *et al,* 1993; Wilkinson D, 1999), with many countries in

this region having experienced a marked increase in tuberculosis notifications (Nunn PP *et al,* 1994). Prevention of tuberculosis is thus important for the reduction of HIV-related morbidity and mortality (especially in developing countries).

#### *1.2.1.2 Increased tuberculosis risk in HIV-infected Adults with Advanced Disease*

HIV is regarded as the most potent activator of tuberculosis. However, the risk is not linear, but increases progressively with advancing immune suppression from HIV disease. The risk of both reinfection and reactivation tuberculosis increases with advancing immune suppression as assessed by CD4+ lymphocyte count (Markowitz N *et al*,1997; Holmes CB, 2006) or clinically advanced HIV disease with WHO Clinical stage 3 or 4 (Wood R *et al,* 2000).

### 1.2.2 Strategy to combat impact of TB/HIV co-infection

The World Health Organization Millennium Development Goals (WHO-MDG) strategy of 85% tuberculosis cure rate and 70% tuberculosis detection rate includes the prevention, management and control of HIV. This strategy could be achieved through intensified community-based interventions and early diagnosis of HIV along with treatment of AIDS and HIV-associated tuberculosis with anti-retroviral therapy (ART). An intensification of the DOTS strategy in managing tuberculosis would also be required (Narain JP & Lu YR, 2004; Maher D *et al,* 2005).

Having a high tuberculosis cure rate and limiting the progression of active tuberculosis (especially among the HIV-infected) through the use of LTBT could play a vital role in the reduction of the tuberculosis incidence. Furthermore, this tuberculosis strategy should be accompanied by

improvements in the socio-economic conditions of more vulnerable groups residing in resource poor settings (Mohammed A, 1995).

### 1.2.3 The use of INH in latent tuberculosis treatment (LTBT)

Various combinations of drug therapy regimens and short course therapy as well as the directly observed short course (DOTS) strategy has been widely used for tuberculosis. However, preventive therapy with isoniazid (INH) has not been used consistently in the developed countries and its use in the developing countries has been rare.

Just at the commencement of the era of HIV there were several recommendations made for those individuals that were recently exposed to MTb or were regarded as high risk individuals. These recommendations were made by the Joint Tuberculosis Committee of the British Thoracic Society (JTBCBTS 1994; Ormorod LP, 1990), the American Thoracic Society & Centre for Disease Control and Prevention (ATC & CDC, 1994; MMWR, 1990).



The Cochrane Systematic Review of Isoniazid preventing tuberculosis in non-infected HIV infected persons (Smeja MJ *et al,* 1999), involving 11 trials (conducted between 1962 – 1994), showed that INH was effective in preventing tuberculosis in 60% of the people when compared to the placebo, [RR 0.40; 95% CI: 0.31 to 0.52)]. This review also showed that the pooled relative risk of outcome of overall mortality was RR 1.10 (95% CI: 0.94 – 1.28), suggesting that INH had no effect on mortality.

Individuals identified as being infected with MTb are termed as having latent tuberculosis infection (LTBI). Prophylaxis for LTBI includes various regimens with varying duration of treatment. Although IPT is recommended by WHO (WHO & UNAIDS, 1998) and is most widely used,

other regimens include the use of Rifampin plus Isoniazid (RH) or Rifampin plus Pyrazinamide (RZ) or Rifampin plus Isoniazid plus Pyrazinamide (*RHZ) or Rifampin (R) alone.*

Tuberculosis Preventive Therapy (TBPT) is recommended (WHO & UNAIDS, 1998) for HIV-infected persons who have tested positive for the tuberculin skin test (TST) and who do not have active tuberculosis. However, in settings where TST is not feasible individuals maybe considered for TBPT if infected with HIV in:

- Populations with high prevalence tuberculosis infections estimate to be 30%
- Health care workers
- Household contacts of TB patients
- Prisoners
- *Miners*
- Other groups at high risk of acquisition or transmission of TB

TBPT has seen several terms used to describe this form of therapy, such as Preventive Therapy (PT) and Latent Tuberculosis Treatment (LTBT). However, these terms are interchangeable and LTBT is a much broader term referring to treatment of latent tuberculosis infection (LTBI) by one or a combination anti- tuberculosis drugs such as INH, Rifampicin (R) and Pyrazinamide (Z). For the purpose of this thesis the term IPT will be used referring to the use of prophylactic INH when referring to the participants enrolled for this trial, unless otherwise indicated. The term LTBT will be used in reference to other studies where it has been stated unless otherwise indicted as IPT.

The use of IPT for those individuals with LTBI remains an effective tool for the prevention of tuberculosis. In the era prior to HIV, LTBT in developing countries was limited to select groups such as household contacts (especially children) who were exposed to active tuberculosis. However, today with the advent of the era of HIV, LTBT in developed countries, especially in the USA, is widely used in the prevention of tuberculosis.

Although the benefit of LTBT appears to be limited to the HIV-infected individuals with a TST-positive status (Bucher HC *et al* 1999; Woldehanna S & Volmink J, 2004), the WHO has recommended the use of INH for LTBT in all HIV-infected individuals in countries where the prevalence of LTBI is greater than 30% and where TST for purified protein derivative (PPD) is not feasible (WHO, 1999). However, it must be borne in mind that INH is not 100% effective and that subsequent tuberculosis exposure could result in the development of tuberculosis despite preventive therapy. Furthermore, IPT would not be able to prevent tuberculosis resulting from the exposure to INH resistant MTb. Also the effectiveness of the INH prophylaxis would largely be dependent on the adherence of the compliance of individuals to whom INH prophylaxis has been prescribed as well as the absorption of anti-tuberculosis drugs in AIDS patients has been shown not to be optimal (Peloquin CA *et al,* 1996).

Before placing the HIV infected patients on LTBT, it is essential to exclude active tuberculosis in order to prevent the development of drug resistance. Tuberculosis screening of these patients is vital. WHO policy on LTBT recommends that all individuals living with HIV be screened for TB (including HIV–uninfected individuals) should be asked if they have had a persistent cough for than two weeks and if their response is in the affirmative, they should be screened for tuberculosis. This is based on the premise that most people with active tuberculosis, especially patients with advanced HIV, have constitutional symptoms. Until a valid screening test is established, the recommendation is that a chest radiograph should be

examined for each tuberculosis suspect patient before considering LTBT (WHO, 1999).

LTBT has been demonstrated in several randomized controlled trials (RCTs) to reduce the risk of development of active tuberculosis in HIV-infected patients, particularly among those with TST positive status. Early INH prophylaxis studies among HIV infected adults indicated that INH is more effective in TST positive patients than in TST negative patients (Wilkinson D, 1999). Further studies conducted show a consistent benefit of preventive therapy among TST positive patients in general but not among TST negative patients (Wilkinson D, 1999; Bucher HC *et al,* 1999; Woldehanna S & Volmink J, 2004)

In the Cochrane Systematic Review including 13 trials of differing HIV target populations and entry criteria, LTBT reduced the risk of tuberculosis by 36% (RR 0.64; 95% CI: 0.51 - 0.81). When INH versus placebo was considered, the tuberculosis risk reduction was 36%, RR 0.67; 95% CI: 0.51 - 0.87 (Woldhanna S & Volmink J, 2004). This review also (Woldhanna S & Volmink J, 2004) demonstrated a tuberculosis risk reduction of 17% (RR 0.83; 95% CI: 0.58 - 1.18) in seven trials of PPD negative patients, which was not statistically significant. However, it must be noted that this meta-analysis did not stratify response by CD4+ lymphocyte count or WHO clinical stage. Currently, there are insufficient data on the efficacy of IPT in patients with advanced HIV disease (WHO clinical stage 3 or 4) and negative TST in TB endemic areas with a high TB and HIV incidence.

The duration of LTBT for 3-6 months could be termed as short-term LTBT. Whereas the duration of LTBT for greater than 6 months could be termed as long-term. Short-term LTBT in HIV infected adults seem to merely delay and not prevent tuberculosis (Quigley MA *et al,* 2001). Another study

(Whalen C *et al,* 1997) showed that the INH duration of benefit was limited. However, neither of these studies were designed to asses this outcome. Although short term LTBT may be more cost-effective (Masobe, P *et al,* 1995) long term LTBT has been recommended (Quigley MA *et al,* 2001). A study by Comstock has shown that INH prophylaxis for 12 months may be better than six months in HIV-negative immunocompromised individuals (Comstock GW, 1999). Fitzgerald and colleagues (Fitzgerald DW *et al,* 2000) presented data suggesting that INH prophylaxis has an effect on tuberculosis infection after treatment of LTBI, that is dependant on the duration of IPT, with long term INH prophylaxis said to be advantageous.

A meta-analysis has shown that a regimen of Rifampicin and Isoniazid administered for three months compared to the regimen of Isoniazid administered for 6–12 months was equivalent in terms of efficacy, safety and mortality (Ena J & Valls V**.** 2005). To date, current literature has not provided any studies that have compared the effect of INH prophylaxis for 6 and 12 months in HIV positive individuals.

In a RCT that compared a 2-month regimen daily rifampin and pyrazinamide with a 12-month daily regimen of isoniazid in LTBT among HIV–infected individuals (Gordin F *et al*, 2000), showed no differences in terms of preventing tuberculosis, efficacy and safety when comparing the 2-month regimen with the 12-month regimen. According to 2005 Centre for Disease Control (CDC, 2005) Guidelines for Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, it is desirable to initiate intermittent LTBT if a patient is TST positive and is at high risk of HIV infection or being in contact with tuberculosis patient.

Although a systematic review of RCTs (Volmink J *et el,* 2006) of DOTS for treating tuberculosis has been conducted, there is a paucity of research on

supervised LTBT as compared to self administered treatment (SAT). Data from a study (Heal G, 1998) with non-random allocation to treatment groups of DOTS versus SAT LTBT demonstrated that adherence had improved as a result of patient supervision. The need for patient nominated supervisors for directly observed LTBT will be further supported with additional findings in the Literature Review chapter.

Thus it is reasoned that whilst focussing on the efficacy of the INH intake it could cause adverse effects and INH resistance. This risk could be reduced by the enhancement of adherence to LTBT with the introduction of a treatment supervisor nominated by the participant prior to the enrolment. This study thus proposes to assess IPT and the intermittent administration of supervised INH prophylaxis in clinically advanced HIV patients with a TST negative status.



## 1.3 Research problem

Anergic patients with advanced HIV disease (WHO clinical stage 3 or 4) were under-represented in previous RCT. To date there are the only two such trials (Rivero A *et al,* 2003; Gordin FM, 1997 *et al*) that enrolled anergic patients with a substantial proportion of AIDS patients. However, these trials were based in developed countries where tuberculosis is not endemic. Hence these results cannot be generalised to developing countries.

The Whalen trial (Whalen CC *et al*, 1997) in Ugandans, had excluded patients with WHO clinical 4, but included some patients with WHO clinical stage 3 and had included a substantial number of anergic patients. This was a trial of three regimens to prevent tuberculosis among adults in Uganda infected with HIV. The tuberculosis incidence rates did not differ

among anergic patients that were administered INH or placebo for six months. The authors speculate the reason why INH among anergic patients did not confer same degree protection as that among TST positive patients could be attributed to drug malabsorption or other host factors associated with advanced disease. But more importantly the sample size of this anergic cohort was small and rendering the benefit of INH of anergic patients inconclusive.

The question whether INH prophylaxis reduces tuberculosis for the patients in developing countries with negative TST (anergic) in HIV-infected adults with clinically advanced disease (WHO Clinical stage 3 or 4) still remains unanswered.



## 1.4 Study rationale

The rationale of preventive therapy is to eliminate LTBI in individuals and thus prevent the development of active tuberculosis. The Cochrane Review of INH prophylaxis among non-HIV infected patients (Smieja MJ *et al*, 1999), proposed that one case of active tuberculosis could be prevented if nine high risk individuals with a positive TST, with silicosis and 20% (or higher) baseline risk of developing active tuberculosis, were administered INH prophylaxis for six months. Based on this premise, the question is: could such a similar benefit be obtained in HIV-infected patients with a negative TST and with a high baseline risk (advanced HIV disease) of developing tuberculosis who reside in a tuberculosis endemic setting?

In (HIV) seronegative persons with LTBI, the lifetime risk of tuberculosis is about 10%, compared with 10% per annum if they are HIV co-infected (Selwyn PA *et al* 1989). Meta-analyses on the treatment of LTBI in HIV-infected adults have shown a significant reduction in the incidence of tuberculosis in participants with a TST, but not in those with a negative

TST (Woldehanna S & Volmink J, 2004; Bucher *et al,* 1999). In HIV-infected patients, TST is more likely to be negative as the CD4+ lymphocyte count declines (Markowitz N *et al,* 1993). The risk of HIV-associated tuberculosis increases with advancing immune suppression, as assessed by CD4+ lymphocyte count or disease stage (Holmes CB *et al,* 2006; Wood R *et al,* 2000). In areas such as South Africa, where tuberculosis is endemic, the majority of HIV-seronegative adults have LTBI, as assessed by a positive TST (Rangaka MX *et al,* 2007). In this setting, most HIV-infected patients with a negative TST will be anergic due to advanced HIV disease, and are thus at high risk of tuberculosis (Holmes CB *et al,* 2006; Wood R *et al,* 2000).

It is therefore surprising that treatment of LTBI has been shown to be ineffective in TST-negative participants in trials conducted thus far (Woldehanna S & Volmink J, 2004; Bucher *et al,* 1999). This lack of effect could be explained by the fact that participants with advanced HIV disease were under-represented in placebo-controlled clinical trials conducted in areas where tuberculosis is endemic (Hawken MP *et al,* 1997; Mwinga A *et al,* 1998; Pape JW *et al,* 1993; Fitzgerald DW *et al,* 2001); TST negative participants were therefore more likely to be 'true negatives', i.e., they did not have LTBI. Tuberculosis incidence in Cape Town, South Africa, exceeds 500 per 100 000 population (Wood R *et al,* 2000; Rangaka MX *et al,* 2007) and the prevalence of TST positivity in HIV-seronegative individuals exceeds 80% Rangaka MX *et al,* 2007). Previously reported study shows an annual tuberculosis incidence exceeding 30% in HIV-infected adult patients with clinically advanced disease ((Wood R *et al,* 2000).

This study is based on the premise that INH preventive therapy in HIV-infected adults with clinically advanced disease (WHO Clinical stage 3 or 4) who were TST negative might be effective in the setting of an endemic area of TB in preventing the development of TB. This study attempted to

enhance the effectiveness of IPT by ensuring optimal adherence. This study took precautions that would reduce the risk of recruiting participants that may have been undiagnosed or misdiagnosed for tuberculosis. A vigorous tuberculosis screening procedure was introduced prior to the patients' enrolment into the trial to prevent treating participants with undetected tuberculosis with INH and thus reducing the risk of INH resistance. This provided an opportunity to validate a questionnaire based on the tuberculosis screening instrument and thus exclude undetected cases of active tuberculosis prior to enrolment of participants to the randomised clinically controlled trial.

## 1.5 Hypothesis of the study

Intermittent and supervised INH prophylaxis will result in a significant reduction of tuberculosis incidence among patients with negative TST and clinically advanced HIV disease (WHO Clinical stage 3 & 4) patients in a setting with a high tuberculosis incidence.

## 1.6 Purpose of the study

The purpose of this study was to investigate the efficacy of IPT, for patients with negative TST and clinically advanced HIV disease with WHO Clinical stage 3 & 4.

## 1.7 Aim of the study

The main aim of this study was to determine the efficacy of intermittent INH supervised prophylaxis in HIV-infected adults with advanced disease (WHO Clinical stage 3 or 4) among participants with a TST negative status

in a high tuberculosis endemic setting, by means of a double blinded randomised controlled trial.

## 1.8 Objectives of the study

### 1.8.1 Primary Objectives

1.8.1.1 To develop and assess the validity of tuberculosis screening instrument for resource poor settings to detect active tuberculosis cases prior to INH/Placebo;

1.8.1.2 To determine efficacy of intermittent directly observed INH prophylaxis in the prevention of tuberculosis in HIV-infected participants with advanced disease (WHO clinical stage 3 or 4) and who are TST-negative

### 1.8.2 Secondary Objectives

1.8.2.1 To compare the number of hospitalization events, CD4 decline and mortality in the INH and placebo groups;

1.8.2.2 To evaluate the adherence of patients to IPT;

1.8.2.3 To compare adherence to IPT in the different patient nominated supervisor categories (e.g. home, community or work-based);

1.8.2.4 To compare adherence to unsupervised Cotrimoxazole with adherence to the intermittent and supervised INH/Placebo among the same participants;

# CHAPTER 2: LITERATURE REVIEW

## 2.1 Introduction

### 2.1.1 Background to tuberculosis control

**I**n 1947, due to the high prevalence of tuberculosis and the global distribution of this problem, WHO (WHO, 1947) was motivated to prioritize it's TBCP by promoting mass Bacillus Calmette-Guérin (BCG) vaccination campaigns (Comstock GW. 1994).

The discovery of Streptomycin in 1944 and its introduction in 1946 as a standard treatment for tuberculosis marked the beginning of chemotherapy for tuberculosis control worldwide (Schartz A & Wakesman SA, 1944). The use of Streptomycin was followed by Isoniazid (INH) in 1952, after the first clinical trial began in 1951 at Sea View Hospital in Staten Island, New York. This was followed by the use of Pyrazinamide (1954), Cycloserine (1955), Ethambutol (1962) and Rifampicin (1963); introduced as anti-tuberculosis agents (University of Medical and Dentistry of New Jersey - UMDNJ, 1996). Further improvements in the tuberculosis control measures were the introduction of INH and Rifampicin (Raviglone MC & Pio A, 2002) in the implementation of short-course chemotherapy regimens (Fox W *et al,* 1999).

In 1959 at the Arden House Conference (in the US), national efforts were refocused on eliminating tuberculosis from America. It recommended nationwide chemotherapy for all persons with active tuberculosis and support for the tuberculosis preventative treatment program for those with LTBI. In1967 the American Thoracic Society recommended that everyone

with a positive TST receive Isoniazid chemotherapy to prevent disease progression. To date, INH chemoprophylaxis (LTBT) is maintained to be one of the most effective regimen for preventing tuberculosis.

The use of INH as treatment for those with LTBI still remains an effective tool for preventing active tuberculosis among the vulnerable individuals. In the era prior to HIV, INH chemoprophylaxis was limited to select groups such as household contacts who were exposed to active tuberculosis and persons with positive TST status in developed countries.

With the advent of the HIV pandemic, INH chemoprophylaxis is now being used in HIV-infected individuals. The WHO guidelines recommend the use of IPT in HIV-infected individuals with a TST positive status or, in countries where the prevalence of LTBI is greater than 30% and where TST for PPD is not feasible (WHO, 1999).



### 2.1.2 Era of tuberculosis prior to the advent of HIV/AIDS in South Africa

In the era prior to the advent of HIV/AIDS, the TBCP in South Africa had tabled a policy on tuberculosis infection control (DOH SA TB Policy Statement, 1979). This Tuberculosis Infection Policy was aimed at reducing the risk of tuberculosis infection in the country to below 0.03% per annum for all population groups and ensuring effective treatment of all diagnosed tuberculosis cases. This goal was in line with the recommendations of international tuberculosis Policy. The goal of this policy was to focus on two phases.

Phase 1 was to manage and control the infectious pool which involved active and passive case finding, short course therapy and BCG vaccination. Phase 2 focused on endogenous reactivation of the infected

pool and involved chemoprophylaxis for positive tuberculin persons, BCG vaccination and continuation of the methods of Phase 1.

It has been estimated that 33% to 70% of close contacts of active PTB cases are subsequently infected. A geographical information system (GIS) evaluating the distribution of tuberculosis in a high-incidence community (Beyers N *et al,* 1996) demonstrated that more than one third of all dwellings had housed at least one tuberculosis case within the decade of the study and within this community tuberculosis cases were spread unevenly and occurred repeatedly in certain houses of that community.

In an investigation of HIV-infected individuals based in a housing facility, 30 were exposed to tuberculosis, of whom 11 (37%) developed active tuberculosis within four months. The number of new TSTs positive for PPD among this group of 30 individuals was determined to be four (13%) (Daley CL *et al,* 1992).

In South Africa it was estimated that 8% of contacts had developed active tuberculosis in the early 1980's (Collins TFB, 1981; Benatar SR, 1982). By 1983 the prevalence and risk of tuberculosis infection in adults were found to be on the decline, with the exception of the Coloured population in the Western Cape (Fourie PB, 1983). The conclusion of this study is still controversial with Packard regarding the tuberculosis decline in the late 1960s as an apparent decrease rather than a true decrease, dubbing this phenomenon an 'optical illusion' (Packard, RM, 1990).

Packard argues that the earlier rise in tuberculosis in the 1950s and the 1960s in South Africa may have been influenced by increased case finding efforts rather than a true tuberculosis increase. Packard argues three points in support of his theory.

Firstly the decrease in tuberculosis notifications after 1965 may be apparent rather than real because the social and economic conditions in urban areas among the disenfranchised (especially Africans) had deteriorated significantly. Secondly, Packard argues that the use of BCG and chemotherapy in curing tuberculosis cases and preventing its spread may have been only marginally effective and it may have contributed to the real rise in tuberculosis (because of poorly managed tuberculosis control programmes). Lastly, he argues that the mass removal of urban Africans resulted not in the decrease of tuberculosis incidence but rather displaced tuberculosis incidence to 'bantustans' or 'homelands' or 'national states' (what has been referred to in South Africa by many as the 'great disappearing act').

By the early 1990s, it was quite evident that the South African TBCP goals were not being achieved. Factors attributing to this failure are numerous. However, the following have been acknowledged as the main factors resulting in failure to achieve the goals of the South African TBCP (Coovadia HM & Benetar SR, 1991).

- Weak Primary Health Care (PHC);
- Poor central coordination of tuberculosis control;
- Insufficient welfare system;
- Lack of community involvement;
- Inadequate support and referral systems;
- Inappropriate health education of health workers;
- Poor integration of health workers into the Tuberculosis Control Programme;
- Insufficient evaluation of the programme;

A slightly different view on the failure in achieving the South African TBCP goals was aptly summed up almost a decade before it occurred, by Glatthaar (MRC Review of TB 1987): *"The eradication of TB in our lifetime is an unattainable dream, and planning must be in terms of decades, not years. Our inability to eradicate TB can be blamed entirely on the unpredictable behaviour of the reservoir of infected persons in the Republic. We are burdened with this huge reservoir of infected persons and we can only decrease the inflow and arrest further expansion of the pool but we cannot control the outflow of the infectious cases."*

### 2.1.3 The advent of the HIV/AIDS era in South Africa

The first diagnosed AIDS case in South Africa was reported in 1982, with HIV infections initially occurring mainly among gay White men. By 1985 it was being reported in other sectors of society. In 1990, the first (of subsequent annual) South African national antenatal HIV survey was conducted, showing 0.8% HIV sero-prevalence. In 1995 at the International Conference for People Living with HIV and AIDS, convened in South Africa, the then Deputy President Thabo Mbeki acknowledged the seriousness of the epidemic. The South African Ministry of Health announced that some 850 000 people (2.1%) of the total population were estimated to be HIV positive (Pope H, 1995). By the end of 2005 there were five and a half million people living with HIV in South Africa, and almost 1 000 AIDS deaths occurring every day (UNAIDS, 2006).

The complacency and inability of the government to set in place innovative preventive strategies and the frustration of health professionals in dealing with the early stages of the HIV epidemic, have been succinctly summed up in a letter to the editor in the Lancet (Carswell W, 1993): *"Since 1984, I have been involved in several aspects of the HIV pandemic, in Africa and elsewhere. Much of this work has been to encourage governments to implement preventive programmes. And in 1991/92, I was a Medical*

*Adviser to the South African Government's AIDS Unit. A depressing feature of this pandemic is the certainty that when HIV arrives in a country the same cycle of responses has to be played out once again. Countries find it difficult to learn from other's mistakes, and South Africa is no exception."*

By 1995, government and health authorities were being alerted to the pending health crisis presented by the increasing tuberculosis incidence and the fact that historic interventions had not made a significant impact. The Western Cape was the epicentre of the tuberculosis epidemic and concerns were raised regarding the advent of HIV and the negative impact this would have on current and future tuberculosis interventions. The global re-emergence of tuberculosis with the advent of HIV/AIDS has been compounded by an increase in MDR-TB. Rising tuberculosis mortality, as well as lengthy and expensive treatment, would not augur well for the new South Africa. It was also repeatedly stated that delay in implementing interventions in the prevention, management and control of TB/HIV would result in the new South Africa facing a catastrophe of an unprecedented magnitude (Mohammed A, 1995).

Failure of the South African Tuberculosis Programme has not only resulted in an increasing number of active infectious tuberculosis cases, but more importantly, it has increased the infected tuberculosis pool by exposing a susceptible population to an increased level of infection. This failure to control the tuberculosis epidemic was further compounded by the inaction of the government in intervening prior to the increase in HIV incidence, resulting in an increasing number of TB/HIV co-infections. In 1996 the Western Cape declared a Provincial Tuberculosis Emergency. This occurred three years after the WHO had declared tuberculosis a global public health emergency (Editorial, CHASA. 1993).

HIV has not only increased the burden of tuberculosis programmes, but has crippled many existing health care delivery services in many high HIV prevalence countries that were already poorly resourced prior the advent of the HIV era. It is essential that the basics of tuberculosis control interventions are implemented in collaboration with HIV control programmes so that HIV-related tuberculosis interventions are prioritized both in respect of treatment and prevention (Maher M *et al,* 2005).

The reason tuberculosis persists as a global problem is summed as follows (Benatar S, 2005): *"Failure to appreciate that the emergence and spread of infectious diseases (afflicting predominantly the poor) are attributable to the ideology and economic forces that perpetuate poverty, will diminish our ability to control HIV/AIDS and tuberculosis and probably favour the emergence of more new infectious diseases."*

### 2.1.4 Development of active tuberculosis in the HIV-infected

HIV not only increases the risk of tuberculosis among those with LTBI (Bucher *et al,* 1999; Woldehanna S, Volmink J, 2004), but also the risk of tuberculosis following primary infection and re-infection (Daley CL *et al,* 1992; Schafer RW *et al,* 1995).

HIV-associated tuberculosis is mainly dependent on three factors. These are the population incidence and prevalence of infection with *Mycobacterium tuberculosis*, the population prevalence and incidence of HIV infection, and the extent to which these two populations of tuberculosis-infected and HIV-infected overlap.

Three components of tuberculosis infection contribute to tuberculosis morbidity. Primary tuberculosis is defined as tuberculosis resulting from a single infection acquired within the past five years. Endogenous reactivation tuberculosis is defined as tuberculosis resulting from a single

infection acquired more than five years earlier. A molecular study of TB latency for several years has shown late onset of TB has been attributed to the endogenous reactivation of dormant bacteria (Lillebaek T *et al*, 2002). Exogenous re-infection TB is defined as TB resulting from a second (or several infections) acquired at any time following the first infection.

The extent to which these different components contribute to the tuberculosis morbidity in the community is largely dependent on the prevailing risk of infection and the age of the population segment concerned. The number of tuberculosis cases and deaths that occur in the future are dependent on how well and how speedily the WHO TBCP can be implemented in countries with a high incidence of tuberculosis.

HIV is the strongest risk factor yet identified for progression from LTBI to tuberculosis. There are several studies that have evaluated HIV as a risk factor for tuberculosis among persons with tuberculosis infection. The first study was in New York City among TST positive injection drug users enrolled in a methadone maintenance program. The risk of tuberculosis was about 8 per 100 person years (Selwyn PA *et al,* 1989).In a multi-center study in Spain, the risk in HIV infected, TST positive patients of developing tuberculosis was about 16 per 100 person years (Gellar A, *et al,* 1993). In a multi-center study in Italy, the risk of developing tuberculosis, among the participants of the study, was about 5 per 100 person-years (Antonucci G *et al,* 1995).

The model developed by Cohen and colleagues (Cohen T *et al,* 2006), shows that the systematic use of IPT to prevent progression infections among HIV-infected individuals and will reduce the local burden of infection and active tuberculosis for several years. However, it is suggested that this benefit would be short-lived by the rapid emergence of INH resistant especially in high IPT coverage areas, where the IPT

program is insensitive to the prevalence of HIV and drug resistant tuberculosis. Hence it is believed that IPT would be best performed in such a setting where intensified diagnosis and treatment of tuberculosis is incorporated at the time of initiating IPT program.

### 2.1.5 Impact of co-infection with HIV on the burden of TB

HIV negative individuals infected with MTb have an estimated lifetime risk of 5-10% of active tuberculosis (Sutherland I, 1976; Vynnycky, E, 1997), as compared to a 50% lifetime risk of active tuberculosis among HIV-infected persons (Pape JW, 2004). The annual risk of tuberculosis in persons co-infected with tuberculosis and HIV has been estimated to be about 10% (Bucher HC *et al,* 1999).

The global targets for tuberculosis control were postponed from 2000 to 2005 and further postponement will be necessary as a result of the HIV pandemic (Harries AD *et al,* 2005). Preventing further infection of HIV is necessary if tuberculosis incidence in this region is to be successfully controlled.

It was estimated globally that there were 8.3 million new tuberculosis infections in 2000, with an incidence rate of 137/100 000 population; ranging from 121/100 000 to 151/100 000. The highest incidence rates of 290/100 000 population per year, (ranging from 265/100 000 to 331/100 000) occurred in the WHO African region (Corbett EL *et al,* 2003), with a 6% annual increase in the number of tuberculosis cases. It was estimated that 9% (ranging between 7%-12%) of all new adult tuberculosis cases (aged 15-49 years) were attributed to HIV infection but in the WHO African Region this proportion three times greater (Corbett EL *et al,* 2003). In the WHO African region, 31% of new adult tuberculosis cases were HIV-infected (Corbett EL *et al,* 2003). Of the 1.8 million deaths from

tuberculosis, 12% (226 000) were attributed to HIV. Tuberculosis in turn resulted in 11% of all adult AIDS deaths (Corbett EL *et al,* 2003).

The overlapping of the tuberculosis and HIV epidemics is more noticeable in sub–Saharan Africa where 70% of co-infected people reside (Corbett EL *et al,* 2003). The co-infection prevalence rate equalled or exceeded 5% in 8 African countries and in South Africa alone 2 million adults were estimated to be co-infected (Corbett EL *et al,* 2003).

Concern has been raised with regards to the infection between susceptibility and MDR-TB of HIV positive patients. Recently, in January 2006, the spectre of a more deadly form of MDR-TB outbreak was reported in Kwazulu Natal, South Africa with alarmingly high mortality rates. This more deadly form of MDR-TB termed as extensive drug resistant tuberculosis (XDR-TB), a form of MDR-TB, is resistant to three or more of the six classes of second-line anti-tuberculosis drugs. Of the 544 patients studied, 221 had MDR-TB. Of the 221 MDR-TB cases, 53 were defined as XDR-TB. Of the 53 patients, 44 had been tested for HIV and all were HIV-positive. Fifty two of the 53 patients died, on average, within 25 days, including those benefiting from ARV drugs. This emphasizes the strong relationship between HIV and MDR-TB and, more recently, HIV and XDR-TB (WHO 2006).

The KwazuluNatal outbreak does not demonstrate a striking relationship between HIV and XDR-TB. It is yet another reminder that patients with advanced immunodeficiency are like canaries in a coal mine. Trends in recent transmission will appear first and foremost dramatically in this group, but it is not clear that HIV infection per se is associated with drug resistant tuberculosis.

HIV increases the risk for reactivation (Selwyn PA *et al,* 1989) of LTBI (Edlin BR *et al,* 1992), in turn resulting in the rapid progression to AIDS (Bucher HC *et al*, 1999, Daley CL *et al* 1992; Shafer RW *et al,* 1995). This in turn increases the MTb transmission rates at the community level (Odhiambio JA *et al,* 1999; Corbett EL *et al,* 2003). The implications of this are that the health of HIV negative persons is under threat not only from the increase of HIV–associated tuberculosis but also HIV–associated MDR-TB (Ritacco V *et al,* 1997; Agerton TB *et al,* 1999; Moss AR *et al,* 1998).

Among immunocomprised HIV-infected persons with LTBI, progression of primary tuberculosis (Edlin BR *et al,* 1992), reactivation (Selwyn PA *et al,* 1989), or reinfection (Small PM *et al*, 1993) with active tuberculosis is much more likely to occur. It has been determined that a CD4 count below 200 cells/unit is a greatly associated risk of development of active tuberculosis (Halesy NA *et al,* 1993).

A study in Cape Town (Wood R *et al,* 2000) demonstrated that HIV-infected patients that were in WHO Clinical stage 3 or 4 had an adjusted risk ratio of 3.4 (95% CI: 1.8 - 6.4) for tuberculosis compared to those in WHO Clinical stage 1 or 2. The risk of developing tuberculosis thus increased markedly with advanced HIV disease. Furthermore, this study also found that the annual risk of tuberculosis in high incidence tuberculosis communities was in excess of 30% in patients with advanced HIV disease (Wood R *et al,* 2000). A retrospective study of miners on four South African gold mines established that the risk of developing tuberculosis doubles within the first year of being tested HIV positive, with an adjusted case rate ratio of 2.11 (95% CI: 1.45 - 3.09) (Sonneberg P, 2005) compared to HIV negative miners.

### 2.1.6 Impact of Co-infection with tuberculosis on HIV

HIV disease progression is accelerated by concurrent immune stimulation (Wodaz, D & Nowak, MA, 1999; Petruckevitch A *et al,* 1998). Opportunistic infections result in bursts of HIV replication that could possibly be contributing to high HIV transmission rates as observed in sub-Saharan Africa (Corbett EL & De Cock KM, 2001). Quinn and colleagues based this theory (Quinn TC *et al,* 2000) on viral loads in plasma and genital secretions that were shown to correlate with each other and with infectivity. This high HIV transmission rate could also possibly be conducive to increase in HIV re-infection that could lead to more rapid progression of HIV to AIDS.

The effect of active tuberculosis on HIV is less well understood. Although earlier *in vitro* studies have indicated that the replication of HIV was induced by *Mycobacterium tuberculosis* (Lederman MM *et al,* 1994; Goletti D *et al,* 1996), clinical and public health findings are unclear (Corbett EL & De Cock KM, 2001). An earlier study indicated that MTb appears to increase HIV replication both systematically and locally (Halvir DV & Barnes PF, 1998). This study demonstrated that some patients, just prior to diagnosis of active tuberculosis, had a substantial rise in HIV viral load.

Furthermore, it has been reported that viral load is higher in HIV-infected patients with active tuberculosis than those without active tuberculosis (Goletti D *et al,* 1996 & Tossi Z *et al,* 2001). A recent study established that tuberculosis was associated with a small adjusted increase in HIV viral load. Although this increase was not regarded as clinically significant in an individual, it was believed to have some effect on HIV disease progression and HIV transmission at population level (Day JH *et al,* 2004).

However, patients in advanced stages of HIV infection (WHO Clinical stage 3 or 4) are rendered more vulnerable to development of tuberculosis

(Markowitz N *et al,* 1997; Wood R *et al,* 1999) by either reactivation or reinfection and have a shorter survival once they have succumbed to tuberculosis.

A cohort study reported that there were higher adjusted mortality and incidence rates of non- tuberculosis opportunistic infections (OIs) among patients with active tuberculosis as compared to those without active tuberculosis attending an HIV clinic in Cape Town (Badri M *et al,* 2001). This study concluded that the onset of tuberculosis in HIV-infected patients is associated with an increased risk of AIDS (adjusted RR 1.65; 95% CI: 1.08 - 2.41, p = 0.02) and death (adjusted RR 2.165; 95% C: 1.29 - 3.59, p = 0.003). This was believed to be as a result of prolonged immune activation induced by tuberculosis, resulting in increased HIV replication leading to accelerated HIV disease progression.

Meta-analysis of LTBT in HIV-infected individuals with a positive TST demonstrated a significant reduction of subsequent tuberculosis incidence but with no significant impact on survival (Bucher HC *et al,* 1999). This could be explained by the fact that HIV-associated tuberculosis incidence may not be high enough to dominate HIV progression rates and mortality at population level (Corbett EL & De Cock KM, 2001). This would be very likely if the impact on HIV disease progression was exclusive to the tuberculosis cases that occurred early in the course of HIV disease, as has been demonstrated in some studies (Badri M *et al,* 2001; Whalen CC *et al,* 2000).

Whilst the prevention of tuberculosis is vital in the strategy for the reduction of HIV-related morbidity, it has been suggested by two studies (Morris L *et al*, 1998; Lawn SD *et al,* 1999), that the effect of tuberculosis on HIV viral load at a population level has a negative impact despite

effective anti-tuberculosis treatment; as has been observed in studies in sub-Saharan Africa of HIV-infected persons.

## 2.2 Latent tuberculosis treatment (LTBT)

### 2.2.1 Tuberculosis intervention control

The intervention, control and management of tuberculosis involves the treatment of confirmed tuberculosis by chemotherapy; the prevention of tuberculosis infection with primary chemoprophylaxis in infants exposed to infectious tuberculosis cases (with no history of TB disease is usually referred as primary prophylaxis); and secondary chemoprophylaxis (LTBT) for those individuals that are asymptomatic and may have been infected and are at a high risk for the development of active tuberculosis.

Prophylaxis is any medical or public health intervention (before the condition occurs) used to prevent rather than treat or cure a disease or infection. Prophylactic measures are divided into those that prevent the development of the disease (reinfection of tuberculosis and thus prevent active tuberculosis) and secondly to prevent the active tuberculosis) when infection has already taken place (reactivation).

Prior to the diagnosis of tuberculosis, the individual may have infected several persons in close contact. In theory it is quite likely that the direct effect of HIV on the epidemiology of tuberculosis that involves reactivation of latent tuberculosis that was acquired prior to HIV infection. However to date no such data is available to suggests this important hypothesis that has distinguished the contribution of latent tuberculosis acquired prior to HIV infection versus latent tuberculosis acquired after HIV infection.

Hence recent LTBI, because of the likelihood of development of active tuberculosis, is regarded as one of the most important public health risk factors. The direct impact of HIV on the epidemiology of tuberculosis involves the reactivation of LTBI acquired prior to HIV infection or the progression to active disease of LTBI acquired after HIV infection (Sutherland I, 1990). The indirect impact is the increased risk of MTb infection and development of tuberculosis among those not infected with HIV (Sutherland I, 1990).

Although IPT will play no major role to the control of global tuberculosis, its role is likely to vary depending on local epidemiology of tuberculosis and relative importance of reactivation of LTBI compared with progression of recent and new disease episodes. Hence in developing countries where tuberculosis is endemic with higher tuberculosis and HIV incidences, the tuberculosis re-infection risk is greater and contributes to increase in active tuberculosis. In such a setting IPT is limited in its effect but could prevent new infection or prevent the rapid progression of new infection to active tuberculosis or both. The study by Casado (Casado JL *et al,* 2002) suggests that re-infection may be the main cause of failure of INH after LTBT in adherent patients. Hence in developing countries where tuberculosis is endemic with higher tuberculosis and HIV incidence, the long term protection against active tuberculosis, the combination of LTBT and ART would be required.



### 2.2.2 Tuberculosis case detection

HIV associated tuberculosis is frequently difficult to diagnose because of the increased proportion of smear negative and extra-pulmonary disease. This is particularly true of patients with clinically advanced HIV disease (WHO clinical stages 3 & 4) who are at high risk of developing tuberculosis (Wood R *et al*, 2000). Thus there is a need to develop and validate simple screening instruments for diagnosing active tuberculosis in HIV-infected

patients (Wkly Epidemiol Rec 1999), which should be capable of detecting tuberculosis in patients with advanced HIV as they frequently have constitutional symptoms.

A screening instrument for tuberculosis should have a high sensitivity and negative predictive value in order to avoid false negatives, if tuberculosis preventive therapy is to be initiated (WHO.Wkly Epidemiol Rec 1999). The WHO and the CDC recommend chest radiographs as part of the screening process to exclude tuberculosis prior to initiating preventive therapy in HIV infection (WHO.Wkly Epidemiol Rec 1999; CDC/MMR 2000). However, they have argued that chest radiographs should be limited to symptomatic patients and probably only those patients whose sputum is smear negative (Harries AD *et al,* 1997). WHO/UNAIDS recommends a chest radiograph to be taken accompanied by medical history and symptom screening for tuberculosis in asymptomatic people before LTBT. A recent study has established that that a chest radiograph for screening is not required (Mosimaneotsile B *et al,* 2003). However, this study has weakness in terms of not using the gold standard sputum culture) for tuberculosis diagnosis. But according to Chintu and colleague (Chintu C & Mwaba P, 2003), not only are chest radiographs expensive in poor resource settings but too few active tuberculosis cases are diagnosed by this method.



Active case finding, BCG, environmental factors, as well as the detection and treatment of LTBI remain important components of the tuberculosis control strategy. Confirmation of TST is universally accepted as the standard method for detecting LTBI (WHO, 1963) using the Mantoux test. The TST has been acknowledged to have certain limitations because antigens present in PPD are also present in BCG and in non-tuberculous mycobacteria (NTM); resulting in false positives commonly occurring (Pai M *et al,* 2004). Mahomed and colleagues showed that among HIV-negative adults, the overall percentage agreement and the kappa score of Mantoux (using both cut-points of ≥ 10mm and > 15mm) with the three

generations of QuantiFERONs were low (Mahomed H *et al,* 2006). Although Mantoux test is regarded as the gold standard to determine the LTBI the QuantiFERON method (blood test for detection of immune responses to tuberculosis infection as an alternative for TST), in place of the Mantoux rest needs to be reviewed in the context of individuals residing in tuberculosis endemic areas with high tuberculosis and HIV incidence who are highly immunocopromised my yield a false negative TST.

Studies suggest that the prevalence of tuberculosis among the HIV-infected sub-population may influence the association between tuberculin reactivity and the risk of tuberculosis (Watkins RE *et al,* 2000). However, in the HIV-infected individual this may not necessarily be the case. The immune response of these individuals has been compromised by HIV and hence they may be unable to mount a delayed response to the PPD used in the TST, possibly resulting in a false negative TST. With HIV infection, the TST will thus underestimate the prevalence of LTBI.

The validity of TST is expressed as the sensitivity, specificity and the positive predictive value (PPV); which in turn depend on the pre-determined cut-off value for a positive test result confirming the presence of LTBI (Menzies RI,2000). The TST cut-off values are influenced by the prevalence of LTBI among the population being tested for Mantoux.Berkel and colleagues concluded that using a 10 mm cut-off value for Mantoux when LTBI prevalence in the population tested was at least 10%, the PPV was more than 75%. With a lower prevalence, a cut-off value of 15 mm was proposed since this yielded a higher PPV with no effect on the negative predictive value (NPV) (Berkel GM *et al,* 2005).

The CDC guidelines for screening for tuberculosis and tuberculosis infection in high-risk populations recommend a cut-off value of ≥ 5mm

induration on the Mantoux test as a positive TST for detecting LTBI (MMR, 1995). High-risk populations with ≥ 5 mm TST reading are defined as (MMR, 1995):

- Persons with recent close contact with person/s who have active tuberculosis;
- Persons who have HIV infection, or risk factors for HIV infection but unknown HIV status;
- Persons with fibrotic lesions on chest radiographs consistent with healed untreated tuberculosis.

## 2.3 Tuberculosis prophylaxis

### 2.3.1 Advantage of tuberculosis prophylactic treatment

Tuberculosis chemotherapy has two effects. At the individual level, it reduces the risk of death from tuberculosis and restores one's health. Epidemiologically, it interferes with transmission, by reducing exposure time in the community and thus the incidence of infection with MTb. Prophylactic treatment is normally defined as the provision of treatment for a person exposed but not yet infected with the aim of reducing the risk of acquisition of infection. Prophylactic treatment thus also reduces the incidence of LTBI. However, LTBI does not meet this definition since individuals are already infected with MTb; prophylaxis here is aimed at preventing active tuberculosis. But in the settings with a high prevalence of advanced immunodeficiency with a negative tuberculin skin test, a period of isoniazid treatment could be either prophylaxis or treatment of undetected latent infection.

### 2.3.2. INH preventive therapy (IPT)

The WHO, in light of the growing tuberculosis epidemic exacerbated by HIV in some settings, has recommended LTBT (WHO/CDS/TB/2002.296) because it is efficacious (Bucher HC *et al,* 1999) and potentially cost effective (Bell JC, 1999). One of the primary reasons for poor LTBT outcomes is poor adherence (Perriens J & O'Brian R, 1995). However, studies have indicated that poor adherence can be overcome with LTBT supervision (Ngamvithayapong J *et al,* 1997; Aisu T *et al,* 1995; WHO Wkly Epidemiol Rec, 1999; Calvacante S *et al* 1999) similar to that of DOTS supervisor.

Before tuberculosis prophylaxis is widely adopted in sub-Saharan Africa, several questions need to be addressed regarding adherence, long term efficacy, adverse effects, resistance, and the danger of treating undetected active tuberculosis with monotherapy. One concern (Quigley MA *et al,* 2001) is that with IPT, tuberculosis in HIV-infected individuals is delayed, rather than prevented especially in settings of high TB prevalence where reinfection makes a major contribution to active disease, and course of IPT of limited duration could be effective in LTBI. Furthermore IPT could prevent new infection or prevent new infection progressing rapidly to disease or both. However, it would be expected not to provide long term protection in the absence of ART.

The study by showed that a 2-month daily course of rifampin and pyrazinamide is similar in safety and efficacy to 12-month daily isoniazid to prevent tuberculosis in TST positive HIV-infected individuals. Despite toxicity being low in both treatment groups, the discontinuation was slightly higher in the rifampin and pyrazinamide (Gordin, F *et al*, 2000). However a multicentre trial for LTBT (Jasmer, RM *et al,* 2002), showed that a 2-month regimen of rifampin and pyrazinamide was associated with increased risk of hepatitis as compared to 6-month regimen of isoniazid.

Although IPT is effective, the limitations can be overcome to achieve optimum benefit that would outweigh the risks. The concern of 9 – 12 months IPT regarding poor adherence (CDC, 1995), can be overcome by assigning latent tuberculosis treatment supervisors (Heal, G, 1998). The second concern to IPT is isoniazid related hepatitis that could result in occasional fatality (Snider DR Jr & Caras GJ, 1992). This can be overcome by liver function test prior to initiating IPT and ongoing monitoring of the patient. The third concern is associated with increased occurrence of peripheral neuropathy in HIV-infected individuals (Bass, JB *et al,* 1994). This can be overcome by supplementing vitamin B12 with IPT. Finally it is believed that effectiveness of INH may decrease as INH resistant of *Mycobacterium tuberculosis increase* (Moore, M *et al*, 1997).

Current recommendations for the duration of LTBT in HIV-infected individuals vary. A recent review (Padmapriyadarsini C & Swaminatrhan S, 2005) highlights the various duration for preventive therapy ranging from 6-12 months of INH daily to short term (2 or 3 months) regimens. To date the efficacy of long-term (>12 months) regimens is currently being investigated. However, WHO continues to recommend self-administered INH for six months. The CDC recommended the administration of INH for nine months. Rifampicin and Pyrazinamide may be offered daily for two months to contacts of patients with INH resistance. The American Thoracic Society recommends INH for 9 months.

Comstock concludes in his review article (Comstock GW, 1999) that:

- 6 months of preventive treatment does not give optimal protection and should not be considered the standard against which to judge the efficacy of short-course combined drug regimens.
- More than 12 months of preventive therapy has not been shown to give added protection against tuberculosis.
- The optimal protection from isoniazid appears to be obtained by 9 or 10 months of treatment.

Furthermore, the US Public Health Service trial suggests that among tuberculosis contacts that total duration of therapy is more important than its continuity (Ferebee SH, 1970)

Meta-analyses (Woldehanna S *et al,* 2004; Buchner HC *et al,* 1999) on LTBT in HIV-infected adults have shown a significant reduction in the incidence of tuberculosis in participants with a positive TST, but not with a negative TST. However, participants with advanced HIV disease were under-represented in the placebo-controlled clinical trials. Two enrolled only asymptomatic participants (Pape JW *et al,* 1993; Fitzgerald DW *et al,* 2001) and no AIDS cases were enrolled in three trials (Hawken MP *et al,* 1997; Whalen CC *et al,* 1997, Mwinga A *et al,* 1998). Only two trials enrolled participants with AIDS, comprising 15% (Rivero A *et al,* 2003) and 23% of their participants (Gordin, FM. *et al,* 1997). Both these two trial were conducted in developed countries. CD4+ lymphocyte counts were recorded in only three studies, with the medians ranging from 230 to 334 cells/μL (Rivero A *et al,* 2003; Gordin FM *et al,* 1997; Hawken MP *et al,* 1997).

The case for INH prophylaxis to prevent active tuberculosis among those with LTBI remains strong in comparison with other drugs used as a preventive therapy. A study of 135 HIV-positive individuals with LTBI that were administered Rifampicin/Pyrazinamine for 2 months were compared to historical controls of INH treatment for LTBI. Although the completion rate of 92% was better in the Rifampicin/Pyrazinamine group as compared to 61% in the historical INH group, 5 individuals were reported to have stopped preventive therapy in the Rifampicin/ Pyrazinamine group due to severe side effects (Narita M *et al,* 2002).

INH as a drug of choice for LTBT has been established in other studies. When IPT was compared with Rifampicin and Pyrazinamide for prevention

of LTBI in HIV-infected people with TST positive for PPD, those in the INH group had 1% risk of developing tuberculosis as compared to the 3.7% risk of developing tuberculosis in the Rifampicin and Pyrazinamide group after 10 months on entry to the study (Halesy NA *et al,* 1993).

However, the overall follow-up after four years of this study established that there was no statistical significant difference between these groups regarding the incidence of active tuberculosis. A multicenter clinical trial conducted to compare the safety and tolerance of the two month regimen of Rifampicin and Pyrazinamide with that of INH for LTBT, found a significant association with an increased risk of grade 3 and 4 hepatotoxicity with the two regimen drug as compared with 6 month INH (OR 8.46; 95% CI: 1.9 - 76.5; p = 0.033) (Jasmer RM, 2002). Since there appears to be no difference in efficacy between INH and the other regimens for preventive therapy for LTBI, INH would be the choice for LTBI because the risk of adverse effects is less as compared to other regimens.

## 2.4 Tuberculosis prophylaxis trials

### 2.4.1 Tuberculosis prophylaxis prior to HIV era

Early tuberculosis prophylaxis trials prior to the HIV era, to establish the efficacy of preventive therapy with INH in reducing tuberculosis, had yielded definitive results. Four controlled clinical trials investigated the efficacy of preventive therapy (Ferebee SH *et al,* 1963; Mount FW *et al,* 1962; Comstock GW *et al,* 1962; Horwitz O *et al,* 1966) with INH in reducing the risk of tuberculosis among persons with presumed long-standing LTBI.

The number of cases emerging during the treatment year was small with wide 95% confidence intervals. Only the study of villagers in Greenland (Horwitz O, 1966) demonstrated more than 60 % protection while the other three trials showed less than 40% protection from tuberculosis (Comstock GW *et al,* 1962; Mount FW *et al,* 1962; Ferebee SH *et al,* 1963). However, the study in Greenland was of a community wide design and not individually targeted IPT. Hence this might be expected to have much greater effect than individually targeted approach because the potential to interrupt TB transmission rather than simply prevent reactivation of reinfection within the individual.

Studies of contacts of newly identified LTBI cases that were most likely infected in the recent past determined that the risk of tuberculosis was considerably higher than that of tuberculin reactors of unknown or long duration (Veening GJJ, 1968; Egsmose TL *et al,* 1965; Ferebee SH & Mount FW, 1962; Bush OB *et al,* 1965).

In the Netherlands Navy, a case among recruits occurred and infected a large number of other recruits (Veening GJJ, 1968). This setting was used to test the efficacy of IPT compared to placebo. The Netherlands study yielded a 92 % protective efficacy, which provided the highest attainable efficacy as compared to 85% in a Kenyan study (Egsmose TL *et al,* 1965) and 75% in the USA (Ferebee SH & Mount FW, 1962 and 25% in Japan (Bush OB *et al,* 1965). However, the study in Japan did not yield statistically significant protection among the contacts. The contacts of newly identified tuberculosis cases who are tested TST positive are likely to have been infected in the recent past.

The risk of development of tuberculosis in this group is considerably higher than those with a positive TST of unknown or long duration (Comstock GW, 1962) as may have been in the case of the IPT study in Japan (Bush

OB *et al,* 1965). The Cochrane review (Woldehanna, S & Volmink, J. 2004) of IPT in non-HIV-infected persons (2005), which included results based on 73,375 participants from 11 trials showed that TB incidence was reduced to 60% and deaths by 71%.

### 2.4.2 Tuberculosis prophylaxis trials in HIV-positive individuals

Whilst it is important to aim for early tuberculosis diagnosis in HIV-infected individuals, another strategy is to minimize the negative impact of tuberculosis on HIV disease progression with the use of prophylactic treatment.

To date, several trials have been conducted to determine the efficacy of LTBT in HIV-positive individuals. The three meta-analyses of such trials that have been undertaken are shown in Table 1. All three (Wilkinson D, Squire SB & Gamer P, 1998; Bucher HC *et al*, 1999; Woldehanna S & Volmink J, 2004) showed a statistically significant reduction in tuberculosis i.e. 43%, 42% and 36% respectively.

The Cochrane Systematic Review (Woldehanna S *et al,* 2004) of treatment of LTBI in HIV-infected persons included 11 randomised placebo controlled trials and found a statistically significant protective effect against active tuberculosis (RR 0.64; 95% CI: 0.51 - 0.81).

However, this protective effect was more pronounced among TST positive patients. Furthermore, studies have shown that with preventive therapy there was a non-significant reduction in all-cause mortality with a more favourable trend in survival among TST positive patients (Woldehanna S *et al,* 2004; de Pino AMF *et al,* 2001).

**Table 1: Efficacy of IPT: Results from three meta-analyses***

| Author | Country | Relative risk (RR) or odds ratio (OR) for LTBT as compared to no LTBT (95% CI) | | |
|---|---|---|---|---|
| | | TST positive | TST negative | Total |
| Wilkinson *et al* (1998) | Haiti, Kenya, Uganda, US | OR = 0.32 (0.19 to 0.51) | OR = 0.82 (0.50 to 1.36) | OR = 0.57 (0.41 to 0.79) |
| Bucher *et al* (1999) | Haiti, Mexico, Zambia, US, Uganda, Kenya | RR = 0.41 (0.24 to 0.71) | RR = 0.94 (0.52 to 1.38) | RR = 0.58 (0.39 to 0.87) |
| Woldehanna & Volmink (2004) | Haiti, Uganda, Kenya Zambia Spain US, Mexico, Brazil | RR = 0.38 (0.25 to 0.57) | RR = 0.83 (0.58 to 1.18) | RR = 0.64 (0.51 to 0.81) |



An observational study (Churchyard GJ *et al,* 2003) among South African HIV positive mineworkers observed the incidence of recurrent tuberculosis between two cohorts in which one cohort received LTBT and the other did not. This study reported that treatment with INH reduced the number of active tuberculosis cases by half (Churchyard GJ *et al,* 2003). The protective effect appeared to be greatest in men with lower CD4+ lymphocyte counts. Where the CD4+ lymphocyte count was below 200 cells/μL, treating five people could prevent one active tuberculosis case as compared to treating 17 people to prevent one active tuberculosis case among the men with CD4+ lymphocyte counts above 200 cells/μL (Churchyard GJ *et al,* 2003). However, goldmines have extremely high incidence of tuberculosis and hence cannot be generalized to other settings.

Casado (Casado JL *et al,* 2002) studied the risk factors for the failure of IPT in HIV positive individuals, administered with INH for more than nine and 12

months. It was shown that persistence of predisposing factors for exposure to tuberculosis infection, such as drug addiction or new prison admissions, was the main risk factor for infection (relative hazard, 3.17; 95% CI: 1.56 - 17, p < 0,001). This study suggests that re-infection may be the main cause of failure of INH after LTBT in adherent patients. Hence in developing countries where tuberculosis is endemic with higher tuberculosis and HIV incidence, the tuberculosis re-infection risk is greater and contributes to increase in active tuberculosis. In such a setting LTBT is limited in its effect but could prevent new infection or prevent the rapid progression of new infection to active tuberculosis or both. Hence in such a setting to ensure the long term protection against active tuberculosis, the combination of LTBT and ART would be required.

As shown in Table 1, IPT has been demonstrated in several RCTs to reduce the risk of active tuberculosis in HIV infected patients, especially among those TST positive. Early INH prophylaxis studies among HIV-infected adults thus indicate that INH is more effective in patients who are TST positive (Wilkinson D, 1999; Pape JW *et al,* 1993; Whalen C *et al,* 1997). Further studies conducted showed consistent benefit of preventive therapy, especially among TST positive patients (Halsey NA *et al,* 1998; Mwinga A *et al,* 1998; Quigley MA *et al*, 2001; Martinez PA *et al,* 2000).

In the Cochrane Systematic Review (Woldehanna S & Volmink J, 2004) of 13 trials (for HIV-infected individuals), preventive therapy (by any anti-tuberculosis drug), reduced the risk of tuberculosis by 36% (RR 0.64; 95% CI: 0.51 - 0.81) when compared with the placebo. When only INH was considered (in the seven of these 13 trials) and compared to the placebo, the tuberculosis risk reduction was 33% (RR 0.67; 95% CI: 0.51 - 0.87) with limited data suggesting that that the initial protective effect against tuberculosis may decline over the short to medium term.

The benefit of INH prophylaxis is short-lived. It has been demonstrated that subsequent to six months preventive therapy the benefit declined after the first year and after 18 months the rates of tuberculosis in the treated and placebo arms were similar (Quigley MA *et al,* 2001). A recent study indicated that the duration of effect of INH is dependent upon the duration of the therapy. Treatment with INH for six months was effective for a median of 8 months, treatment for 12 -24 months was effective for 22 months; and for those receiving 24-36 months of IPT, duration of effect was 40 months. The results of this study were statistically significant (Fitgerald DW *et al,* 2000).

The first IPT trial in HIV-infected patients (Pape JW *et al,* 1993) showed the efficacy of 1-year IPT in symptom free HIV positive patients with a protective effect (RR 0.62; 95% CI: 0.39 - 0.97) with a median follow-up of 1.8 years for both TST positive and negative participants. Quigley (Quigley *et al,* 1998) reported diminishing protective effect of INH over time. In the study by Quigley (Quigley *et al,* 1998), it was reported that the cumulative risk of tuberculosis in the first 2.5 years was lower in the INH group (RR 0.52; 95% CI: 0.27 -1.00, p = 0.046) than in the placebo. A significantly lower risk of active tuberculosis after a mean of 15 months of IPT was demonstrated in participants with TST positive status, (RR 0.29; 95% CI: 0.12 - 0.67) (Whalen *et al,* 1997). It was noted in this study that the long term benefit remained statistically significant for the Rifampicin regimen but not for INH.

Of the of 13 preventive therapy trials (Woldehanna S & Volmink J, 2004), only seven were INH placebo trials (Hawken MP *et al,* 1997; Mwinga A *et al,* 1998; Pape JW *et al,* 1993; Whalen C *et al,* 1997; Fitzgerald DW *et al,* 2001; Gordin, FM *et al* 1997; Rivero A *et al,* 2003), with only three trials having included only TST negative individuals (Fitzgerald DW *et al,* 2001; Gordin, FM *et al,*1997; Rivero A *et al,* 2003). Two trials included only anergic individuals (Gordin, FM *et al,* 1997; Rivero A *et al,* 2003).

Whereas in the Whalen trial (Whalen C *et al,* 1997), which excluded advanced HIV diseased patients where the negative TST anergic patients were randomly assigned to INH or placebo (RR 0.86; 95% CI: 0.59 – 1.26) which compared the efficacy of different anti-tuberculosis drugs (i.e. INH and Rifampin or INH, Rifampin and Pyrazinamide or INH or Placebo).

However all the participants in the Gordin and Rivero trials (Gordin, FM. *et al*, 1997; Rivero A *et al,* 2003) were symptomatic, anergic and TST negative with RR 0.48 (95% CI: 0.12 - 1.91) and RR 0.66 (0.19 – 2.31) respectively.

Whilst the Gordin trial (Gordin, FM. *et al*, 1997) involved INH and placebo only, the Rivero study (Rivero A *et al,* 2003) evaluated the risk of developing tuberculosis with any of anti-tuberculosis regimens. The relative risk of INH treatment with the various regimens versus no treatment was for 6INH vs. 3HR 1.09 (95% CI: 0.22 - 5.41); 6INH vs. 2RZ 2.76 (95% CI: 0.29 - 0.26); 6INH vs. no treatment group (NT) 1.07 (95% CI: 0.24 - 4.80); 3HR vs. 2RZ 2.53 (95% CI: 0.26 – 0.24); 3RZ vs. NT 0.98 (95% CI: 0.22 – 4.4) and 2RZ vs. NT 0.39 (0.04 -3.48).

The wide 95% CI confirms that the sample size was too small to make any definite conclusions about efficacy of LTBT of anergic HIV-infected patients, especially the 6INH vs. NT (placebo).

Furthermore, no distinction was made among patients on the trial regarding their WHO Clinical stage of HIV infection of the participants. More importantly the Rivero trial (Rivero A *et al,* 2003) was conducted in Spain in a low tuberculosis incidence setting and the results cannot be generalised for developing countries where tuberculosis is endemic.

The Gordin trial involving anergic HIV-infected persons who were at a high risk for development of tuberculosis (Gordin, FM *et al,* 1997) concluded that INH was not efficacious. This trial included children aged 13 years and older with a study population consisting of 33% females was conducted in the US making it difficult to infer conclusions to developing countries. The diagnosis of primary tuberculosis in children in this trial required a different diagnostic protocol to that of pulmonary tuberculosis in adults making the study difficult to infer to adults. The diagnosis in children is not only difficult, but imprecise (Schaaf HS *et al,* 1995).

Hence, it is very likely that some of the primary tuberculosis cases in this trial could have been missed despite the paediatric definition was used consistently in both arms of the Gordin trial. Therefore while misclassification may not have occurred, there is no reason to suspect that this occurred in a differential fashion between the two randomized arms. Finally, not but most cases of active TB in this trial were culture positive.

The Gordon's trial (Gordin, FM *et al,* 1997) showed that the placebo group had a higher proportion of people who had been unemployed for year or more and also included a higher proportion of people who had lived with a person with active tuberculosis for one year or more at the time of enrolment for Gordin's study. This possible bias and the fact that this study was conducted in a low tuberculosis incidence setting render the conclusion of the Gordin's study debatable.

The Whalen trial (Whalen C *et al,* 1997), fails to answer whether INH preventative therapy would benefit HIV-infected adults with clinically advanced disease (WHO Clinical stage 3 or 4) who were TST negative, since it had excluded HIV patients with advanced disease from its trial.

### 2.4.3 Tuberculosis prophylaxis trials in TST negative HIV-positive adults

People infected with MTb and have a positive TST have greater risk of developing active tuberculosis as compared to those people not infected with MTb (Watkins RE, Brennan R & Plant RJ, 2000). However, the proportion of TST negative individuals with LTBI is higher in HIV positive individuals than those who are not infected with HIV (Daniel T, Boom WH & Ellner JJ (2000). Thus the treatment of LTBI has been shown ineffective (RR 0.83, 95% CI 0.58 to 1.18.) in TST negative participants in the seven trials conducted to date (Woldehanna S & Volmink J, 2004, Bucher HC *et al,* 1999). Table 2 summarizes the outcome of these seven trials.

The possible reasons for this lack of efficacy of INH in the treatment of LTBI in TST negative participants in previous trials has already been covered (please refer the section 1.4 of the Introduction chapter. But importantly the two (Gordin, FM. *et al*, 1997; Rivero A *et al,* 2003) which included symptomatic, anergic and TST negative participants made no distinction of participants on the trial regarding their WHO Clinical stage of HIV infection and cannot be generalised to developing countries where tuberculosis is endemic.

Only two trials enrolled patients with AIDS (Table 2), comprising 15% (Rivero A *et al,* 2003) and 23% of their participants (Gordin, FM. *et al,* 1997). CD4+ lymphocyte counts were recorded in three studies: medians ranged from 230 to 334 cells/μL (Rivero A *et al,* 2003; Gordin FM *et al,* 1997; Hawken MP *et al,* 1997). Thus the IPT efficacy of HIV-infected WHO Clinical stage 3 or 4 with TST negative patients have to date as yet not been conclusively established with a greater deal of probability.

**Table 2: Relative Risk of Tuberculosis in INH/Placebo Trials of HIV-infected TST negative adults**

| Author | Median CD4 at baseline cells/μL | HIV Symptoms | AIDS | RR of TB (95% CI) |
|---|---|---|---|---|
| Pape JW *et al,*1993 | ND | Asymptomatic | 0% | 0.70 (0.15, 3.28) |
| Hawken MP *et al,*1997 | 334 | 8.5% Thrush | 0% | 1.31 (0.54, 3.20) |
| Whalen C *et al,*1997 | ND | 28% Thrush/Zoster | 0% | 0.86 (0.59, 1.26) |
| Mwinga A *et al*,1998 | ND | 3.7% Thrush | 0% | 0.77 (0.39, 1.51) |
| Gordin D *et al,* 1997 | ND | Symptomatic | 23% | 0.66 (0.19, 2.31) |
| Fitzgerald DW *et al,*2001 | ND | Asymptomatic | 0% | 1.32 (0.38, 4.56) |
| Rivero A *et al,* 2003 | 230 | Symptomatic | 15% | 0.74 (0.30, 1.79) |

ND = Not displayed



Besides the small proportion of AIDS participants WHO Clinical stage 3 or 4 with TST negative patients in the Rivero and Gordin trials (Rivero A *et al,* 2003; Gordin, FM. *et al,* 1997), these two trials conducted in developed countries, cannot be generalised for developing countries, especially where tuberculosis is endemic and where there is a high rate of HIV and tuberculosis.

## 2.5 Adherence and adverse effects of INH

### 2.5.1 Adherence

This section deals with adherence of INH prophylaxis and studies highlighting improved adherence among symptomatic tuberculosis patients and the complications that could result from non-adherence. But more importantly in order to reduce the risk of resistance from IPT it is more important to exclude active TB prior to starting IPT. The need to monitor adherence and adverse effects and toxicity of INH is of paramount importance. However this needs to be balanced whilst still focusing on the need to ensure that the benefit of IPT outweighs the risk of adverse effects in patients.

In the case of symptomatic HIV-infected patients, tuberculosis treatment adherence may be better than asymptomatic HIV-infected patients, A Thai study (Ngamvuthayapong J *et al,* 1997) confirmed that adherence with INH prophylaxis was better in symptomatic patients. A Kenyan study reported poor adherence in those patients who were only mildly immunosuppressed (Hawken MP *et al,* 1997).

Regarding supervised therapy of tuberculosis patients, the estimated lifetime mortality rates (including deaths from relapses and subsequent complications) of HIV negative individuals with smear positive tuberculosis were estimated to be 5% to 15% among those treated by DOTS, as compared to 10% to 30% in those individuals that were not treated with DOTS (Dye C *et al,* 1999; Mallory KM *et al,* 2000).

Non-adherence to tuberculosis treatment is one of the major factors in the development of relapse (Weis S *et al,* 1994; Havlir DV & Barnes PF, 1999). Furthermore, HIV seropositive patients who received tuberculosis

treatment as outpatients had high rates of non-adherence (Rocha M *et al,* 2003). Those that were non-adherent had an OR (for no tuberculosis cure) of 29.2 (95% CI: 2.43 - 350.1). Non-adherence was the strongest determinant associated with no tuberculosis cure or death (Rocha M *et al,* 2003).

Because of prolonged administration of LTBT, the risk of adverse effects (especially to the liver) is of great concern. Although poor adherence could theoretically lead to INH resistant tuberculosis, there is no data to support this statement. However, it is more important to exclude active undiagnosed tuberculosis prior to starting IPT monotherapy, which may generate INH-resistant MTb. Unsupervised INH preventive chemotherapy for six months in two suburbs in Cape Town, South Africa reported poor adherence (Marais BJ *et al,* 2003). These studies highlight the strategies needed to enhance adherence by shortening the duration of IPT and/or supervision of IPT. Intensification and improved treatment literacy for those patients that have been selected to be on IPT could be another way to promote and enhance adherence to IPT.



A study conducted in Thailand, reported that TST status was not a predictor for adherence to LTBT once therapy commenced (Hiransuthikul N, 2005). However, a higher drop-out rate was associated for LTBT prior to commencement of therapy in this study. When this group was compared to the control group that was administered LTBT without conducting a TST, the adherence to LTBT was estimated to be 84.5% and 79.7% respectively, but with no significant difference in adherence between the two groups. Furthermore, this study also reported a good correlation between adherence measured by pill counts and self-report.

Of the INH and placebo controlled trials of TST negative patients, Pape and colleagues made no mention of any difference in adherence in

patients on the daily self administration of INH and B6 as compared to B6 (placebo). These patients and adherence were clinically assessed at intervals of three months for 12 months (Pape JW *et al,* 1993).

The study by Hawken (Hawken MP *et al,* 1997). of daily self administration (SAT) of INH for six months based on three adherence measures (pill count, patient report of defaulting and urine analysis) showed good agreement between the three categories of adherence i.e. adherent, mildly non-adherent, moderately non-adherent groups (Hawken MP *et al,* 1997). However, this study should be viewed with caution since in the INH group only 145 (45%) patients had tested positive for presence of INH, and no analysis of the incidence of tuberculosis among those who were poorly or non-adherent was performed. In another study (Whalen CC *et al,* 1997), INH was self-administered for six months and evaluated monthly for adherence. Adherence was compared by four different methods: by monthly scheduled visits, self reports, urine tests for INH as well as random INH urine tests of unscheduled visits of patients on INH. Of the 1754 (90%) patients tested, 75% tested positive for INH and of the 97 randomly tested for INH, 78 (80%) tested positive for INH, with higher proportion on scheduled monthly urine tests as compared to unscheduled tests (82% versus 46%, $p < 0.001$) (Whalen CC *et al,* 1997).

The Gordin study (Gordin, FM *et al,* 1997) which also involved self administration of INH or placebo and where each group also received B6 on a daily basis for six months, makes no mention of adherence. Another RCT with twice weekly intermittent self administration of INH for 12 months used pill count as a means of measuring adherence (Pape JW *et al,* 1993); 777 (74%) were adherent, 718 (92%) were probably adherent and 59 (8%) possibly adherent.

A further RCT compared three regimens with the no treatment group (Rivero A *et al,* 2003), where INH self administered daily for six months, was one of the regimens. Patients were evaluated every 15 days for two months and thereafter on a monthly basis. Although adherence was assessed by the doctor in a patient oral interview, report of adherence data in this study was not given (Rivero A *et al,* 2003). The Fitzgerald *et al* study (Fitzgerald DW *et al,* 2001), which involved the self administration of INH on a daily basis for 12 months with monthly visits and thereafter at three monthly visits, also makes no mention of measurement of adherence.

### 2.5.2 Adverse effects and toxicity of INH

As INH has been shown to have minimal risk of adverse effects, the benefit of INH in LTBT far outweighs the risk of minimal adverse effects as can been noted from the following studies. In a meta-analysis (Ena J & Vallis V, 2005) a shorter course of preventive therapy was compared as an alternative to the standard INH therapy and found that both regimens were equally effective where low tuberculosis transmission setting could likely influence the effect of duration of IPT. The short course therapy with two drugs was equivalent to standard INH with regards to efficacy (pooled risk difference 0%; 95% CI: -1% - 2%); severe side effects (pooled risk difference -1%; 95% CI: -7% to 5%) and mortality (pooled risk difference -1%; 95% CI: -4% - 2%).

A study by Mitchison (Mitchison DA, 1985) graded six anti-TB drugs (Pyrazinamide, Thioacetazone, Ethambutol, Streptomycin, Rifampicin and Isoniazid) based on three properties. These included the ability to prevent drug resistance, the killing ability of the drug in early bactericidal activity and the drug sterilizing activity. This study ranked Isoniazid the highest in its ability to prevent INH resistance (when active undiagnosed TB was excluded prior to starting IPT monotherapy), and its early bactericidal

activity in comparison to Rifampicin, Ethambutol, Streptomycin, Pyrazinamide and Thioacetazone (in the pre ART era). As for the drugs sterilizing activity, Isoniazid was ranked third, with Pyrazinamide ranked second and Rifampicin ranked as first. This indicates that, isoniazid is highly effective at preventing the emergence of resistance to other drugs in a multi drug regimen such preventing the emergence of rifampicin resistance. Also data from a very early trial of isoniazid monotherapy for active tuberculosis suggested that higher doses of isoniazid modestly decreased the rate of emergence of isoniazid resistant strains. However, this rationale may not be applicable to IPT.

Concern has been raised regarding the adverse effects of INH.A seven year survey from a Public Health Tuberculosis Clinic where INH was used for LTBT determined that the rate of INH hepatoxicity was lower than previously reported (Nolan C *et al,* 1999). An earlier study had demonstrated that the risk of hepatitis resulting from the administration of INH in the first two to three months was the greatest (Riska N, 1976). A recent study has demonstrated that INH was tolerated by all in the study and that hepatotoxicity was not a major problem among patients that were administered INH (Agarwal SK, 2005; Sadaphal P, 2001; Wilkinson D, 2000). When one considers the benefit outweighing the risk of adverse effects in patients in terms of tuberculosis preventive therapy, the drug of choice would be INH.



In the seven INH placebo RCTs of HIV-infected patients (Pape JW *et al,* 1993; Hawken MP *et al,* 1997; Whalen C *et al,* 1997; Gordin, FM *et al,* 1997; Mwinga A *et al,* 1998; Fitzgerald DW *et al,* 2001; Rivero A *et al,* 2003), adverse effects were minimal (RR 1.66; 95% CI: 1.09 – 2.51).

The Rivero and Whalen studies (Rivero A *et al,* 2003; Whalen C *et al,* 1997), the adverse effects reported in the INH group were minimal did not have

statistically significantly higher adverse events which led to stopping treatment of trial the participants. The relative risk of adverse effects in the PPD positive and negative groups were RR 12.07; 95% CI: 0.69 – 210.76 (Rivero A *et al,* 2003) and RR 2.60; 95% CI: 0.27 – 24.88 respectively. The RR for anergic group in the Whalen study was no estimable (Whalen C *et al,* 1997). Pape (Pape JW *et al,* 1993) had no participants withdrawn as a result of adverse effects or laboratory reported abnormalities. No statistically significant adverse effects were observed in the Hawken trial (Hawken MP *et al,* 1997) where the adverse effects was compared to the placebo with RR 2.20 (95% CI: 0.77 - 6.26), with a few cases of mild reversible hepatitis were reported and no reported cases of clinical hepatitis.

However, of the 1631 participants evaluated during routine tests, seven clinical hepatitis cases were reported in the Whalen trial (Whalen C *et al,* 1997). Six of these cases were anergic TST positive (5 received INH, R and Z). Only one TST positive case received only INH. The cumulative incidence of reported adverse events for placebo of 22 (6.8%) and INH of 31 (7.8%). In this same study, 43 patients had to discontinue treatment with the number of adverse events reported in the TST positive treatment group greater than that in the placebo group and greatest in the group receiving Pyrazinamide.

In the Gordin study (Gordin FM *et al,* 1997), there was no difference between the 29 (11.2%) and 30 (11.7%) reportable adverse events in the INH and the placebo groups. Nine percent in each group of this study, discontinued treatment due to adverse effects of INH, where more than 50% of these patients discontinued during the first two months. A total of 29 (3%) participants were withdrawn from the Mwinga study (Mwinga A *et al,* 1998) because of adverse reactions. Four of these 29 patients were withdrawn because of raised liver enzymes (of which three received INH and one Pyrazinamide); seven with rash (of which one received INH and six Pyrazinamide); 11 with gastrointestinal symptoms (of which one

received placebo, five INH and five Pyrazinamide); and seven with various other complaints (of which two received placebo, three INH and two Pyrazinamide).

In the Rivero trial (Rivero A *et al,* 2003), 34 patients experienced side effects that led to their withdrawal from the trial. However there were no significant differences between the treatment groups. Of the nine patients with hepatoxicity, only one was removed from the 6-month INH treatment group, as a result of symptomatic hepatitis. The remaining eight patients were removed as a result of asymptomatic hepatitis (four of these participants wee treated with the Rifampicin and Pyrazinamide regimen) that showed an increase in transaminases that were 3-fold higher than basal value in the absence of symptomatic hepatitis.

The Fitzgerald study (Fitzgerald DW *et al,* 2001) made no mention of adverse effects due to treatment. As with any drug, there is a therapeutic margin constituted by the difference between the minimum drug concentration for inhibition of MTb and the maximum concentration that can be administered without inducing adverse effects (drug toxicity). This therapeutic margin varies for different anti-tuberculosis drugs (Peloquin CA *et al,* 1999; Acocella G, 1978; Pahlka R *et al,* 1999; Davidson PT *et al,* 1986; Grosset J *et al,* 1970; Zierskie M, 1981).

Some studies have shown that difficulties with IPT include poor adherence (O'Brian RJ & Perriens JH, 1995), hepatoxicity (Byrd RB *et al,* 1979) and the development of isoniazid resistant bacteria (Pablo-Mendez A & Ravigione MC & Laszlo A, 1998).

However, the results of the meta-analysis (Ena J & Vallis V, 2005), one can conclude that short course therapy with two drugs (INH and

Rifampicin) is equivalent to standard INH had no difference in terms of efficacy, proportion, with severe side effects and mortality. Furthermore, the adverse effects to INH are minimal and that hepatotoxicity is not considered a major problem among patients that were administered INH and monitored regularly.

Thus based on this study (Ena J & Vallis V, 2005), and previous studies (Martinez, PA *et al,* 2000; Whalen CC *et al,* 1997) both in RCT and IPT programmes, one can conclude that use of INH prophylaxis outweighs the risk to the patient when administered correctly with regular monitoring both in terms of clinical and/or biomedical monitoring. However, one should note that the risk to the individual could vary substantially depending on age and risk of liver disease and that the potential benefits similarly will vary depending on the estimated risk of developing tuberculosis.

IPT is regarded safe with minimal intervention cost that has the potential to reduce morbidity and mortality resulting from development of tuberculosis especially in HIV-infected individuals (Baicells ME *et al,* 2006). The main cause for INH resistance is because of inadequate diagnosis and treatment of active tuberculosis prior to initiating IPT. Hence the risk for any small increase of INH resistance attributable to IPT should be weighed against the benefit of reducing tuberculosis among the given population in their respective settings. Twice weekly dose of INH (intermittent) may be substituted for daily does of INH, provided a nurse or health care worker or latent treatment supervisor observes and record the ingestion of the medication as prescribed (Schwartzman, K, 2002).

## 2.6 Patient supervision

### 2.6.1 DOTS as part of the global plan to stop tuberculosis

The number of tuberculosis cases and deaths that will occur in the future will depend on how well and how quickly the WHO recommended tuberculosis control strategy is implemented. WHO predicts that in the period between 1997 and 2020, 39 million infections and 17 million deaths can be prevented in Southeast Asia, sub-Saharan Africa and the Western Pacific. This staggering number of cases and deaths could be prevented only if it is feasible to achieve complete implementation of the DOTS strategy by the year 2010. Enormous efforts thus lie ahead for the world community to improve the epidemiologic situation of tuberculosis and to alleviate human suffering and prevent unnecessary deaths.

The Global Plan to Stop TB for 2001-2005 has been extended to continue from 2006-2015 and is to incorporate three key events: (Editorial: Int J Tuberc. Lung Dis, 2006):

- Incorporation of tuberculosis control among the top public health priorities within UN Millennium Development Goals (MDGs)
- The decision by WHO to enhance the DOTS strategy and launch the new Stop TB Strategy, built around DOTS but going beyond it
- The decision in May 2005 by the 58$^{th}$ World Health Assembly (WHA) to foster sustainable financing for tuberculosis control

It is not surprising to note that that one of these three key events includes the enhancement of DOTS, thus emphasizing the vital importance of this essential component of the tuberculosis control, prevention and management strategy of the new Global Plan for Tuberculosis.

### 2.6.2 Directly observed treatment short course chemotherapy

DOTS was introduced by WHO in 1997/8 as a Tuberculosis Control strategy with implementation in all 22 high tuberculosis burden countries identified (WHO, 1998). By 2002, the DOTS Strategy had been implemented in 25 more countries, resulting in 69% of the world's population covered by DOTS. Of the 3 million tuberculosis cases treated by DOTS globally, 1.4 million were confirmed to be smear positive cases. This was in contrast to the total of 13.3 million tuberculosis cases (including 6.8 million smear positive cases) treated by DOTS during 1995-2002 (WHO Global TB RPT, 2004).

The global treatment success rate of DOTS in 2000 and 2001 was reported to be 82%. In 2002 there were 98% tuberculosis cases covered by DOTS in South Africa, compared to 43% in 1999. However, the treatment success rate by DOTS strategy in 2001 was only 58% as compared to 39% under the non-DOTS strategy in the same year. The six most important constraints for not being able to reach targets for case detection and cure in South Africa are (WHO Global TB RPT, 2004):

- Poor laboratory infrastructure
- Human Resources
- HIV/AIDS
- Political Commitment
- Monitoring
- Decentralization of Health Services



### 2.6.3 Treatment supervisors for DOTS versus LTBT

Whilst the DOTS supervisor supervises the administration of tuberculosis medication to individuals on tuberculosis treatment, to enhance good adherence, the LTBT supervisor supervises the administration of tuberculosis prophylaxis to individuals at risk of developing tuberculosis.

The introduction of effective LTBT treatment supervisors in the control of tuberculosis in South Africa could at the very least mitigate the negative impact of the six constraints (i.e. laboratories, human resources, HIV/AIDS, political commitment, monitoring and decentralization of health services) inhibiting the achievement of set tuberculosis targets. With the introduction of the LTBT treatment supervisors, a reduction of active tuberculosis could result. This could result in the reduction of the number of laboratory diagnosis and thus the LTBT treatment supervisors, would not only be complimenting the existing health professional staff but at the same time assist in the decentralising the health services by making it more accessible within the communities. But more importantly it would translate the political will into action whilst at the same time the LTBT treatment supervisors could be catalyst to the HIV/AIDS campaign.

However, a study (White MC *et al,* 2003) to determine the effect of directly observed preventive therapy supervisors for patients with LTBI showed that after having controlled for sex, age and race, the patients on directly observed preventive therapy supervisors were nearly twice as likely to complete IPT (OR 1.93; 95% CI: 1.25 - 3.00) as compared to the patients that were in the self-administered treatment group. Furthermore, 70.3% patients in the directly observed preventive therapy supervisors' (DOPTS) treatment group were reported to have completed therapy as compared to the 47.9% patients in the SAT group. This difference in completion of preventive therapy between the two groups was statistically significant ($p < 0.001$).

There is a paucity of studies of IPT supervision especially among HIV-infected individuals. This may be attributed to the fact that individuals with LTBI are not sick (and are asymptomatic) and may not be motivated to take their medication by SAT or DOTS. Unlike the individuals being supervised by DOTS where both the supervisor and patient who is

symptomatic) associate the compliance to the medication as a means to them being rendered asymptomatic and being cured of tuberculosis.

In addition to this reason, various risk factors activating LTBI such as HIV, social conditions, homelessness and alcohol abuse (CDC, MMR Wkly Rpt, 2000), may have contributed to placing the focus and research on IPT supervision among the vulnerable groups, low on the priority list. In our INH/placebo trial we have attempted to overcome some of these challenges with participants requiring to nominate their supervisor for IPT whilst still maintaining the confidentiality of the patients' HIV status, where it was required to do so,

The DOTS supervisor may be a lay health worker (LHW). They may be selected or nominated from the community and may or may not be remunerated. The DOTS supervisor is supported by the health system, whilst not forming part of it (Kahssay H *et al,* 1998; Lewin SA *et al,* 2004). The DOTS supervisor ensures adherence support and supervision of tuberculosis therapy. In contrast, the LTBT treatment supervisor manages those patients that have not yet, but are identified as being at great risk of developing tuberculosis. Supervision is needed to enhance adherence, since it maximizes the effectiveness of IPT and increase the probability of the successful completion of preventative therapy. Both patient and IPT supervisor are informed of the great risk of development of tuberculosis and the need to be adherent. The treatment supervisor for IPT has a similar role.

To date, two RCTs have not conclusively determined the impact of DOTS on treatment outcomes (Kamolratanakul P *et al,* 1999; Walley JD *et al,* 2001). A RCT conducted in South Africa (Zwarenstein M *et al,* 1998), found that the DOTS supervision and SAT in new patients had the same treatment outcomes. However, for re-treatment cases, those patients

treated with DOTS showed significantly poorer results than those assigned to SAT.

In cases where tuberculosis patients were given the opportunity to choose their treatment supervisor, the treatment outcomes showed an improvement, especially in resource poor settings and among re-treatment cases (Lienhardt C & Ogden JA, 2004, Kironde S & Meintjies M, 2002). The most recent unblinded cluster RCT that evaluated impact of lay health care workers on tuberculosis control programmes among farm worker patients showed that the successful treatment completion rate among the supervised group was significantly better (18.7% improvement, p = 0.042, 95% CI 0.9-3.64) than in the SAT group (Clarke M *et al*, 2005).

A Cochrane Review (Volmink J *et el,* 2006) of DOTS for treating tuberculosis concluded that the treatment outcomes were similar for participants in the DOTS and SAT arms with no significant difference for people cured (RR 1.02; 95% CI: 0.86 – 1.21); cured or completed treatment (RR 1.06; 95% CI: 1.00 – 1.13); or those who had completed their treatment. This review also concludes that there was no rigorous evidence that supported the DOTS prophylaxis for persons with LTBI.

The authors have acknowledged that bias may have influenced the results in some of the DOTS trials where only four trials were adequately blinded and only three involved the blinding of the outcome assessors. Furthermore, the factors that determine the usefulness of DOTS in various settings and the quality of the interaction between the DOTS supervisors and the patients explored. Nor was the quality of clinic supervision and follow-up of patients evaluated. Despite the findings from Cochrane Review on DOTS (Volmink J *et el,* 2006), DOTS still remains the cornerstone of the TBCP.

However, despite the Cochrane findings, programmatic evidence of studies of the effectiveness of DOTS in China showed that the global target of an 85% cure rate was quickly achieved, and the level of drug-resistance was probably reduced by this project. However, case-detection did not reach the 70% global target (Xianyi C *et al,* 2002). The DOTS program in Peru has been a model of DOTS implementation with regard to reaching the WHO targets of 70% case detection and 85% cure. Peru's DOTS program can now also be held as an example among high-burden countries of what is feasible in terms of reducing numbers of cases and deaths (Sua´rez PG *et al,* 2001).

We are of the belief that LTBT treatment supervisor, like the DOTS supervisor, does not dilute the responsibility of the clinic for patient management, patient care and record keeping. The DOTS or LTBT treatment supervisor supplements the health care facility (Dudley L, 2003).

The DOTS strategy includes the following components and implementation approaches:

- Political commitment with increased and sustained financing
- Case detection through quality-assured bacteriology
- Standardize treatment with supervision and patient support
- An effective drug supply and management system
- Monitoring and evaluation system and impact measurement

Thus the LTBT treatment supervisor's role with the direct observation of the standardized treatment with supervision and patient support compliments one aspect of the DOTS strategy. This is contributes to the improvement and enhancement of patient treatment outcomes as well as the involvement of patient care by DOTS/LTBT supervisor, in the community and workplace, as an extension of some of the basic clinic

services that has been made more accessible to patient within the community. Thus the DOTS/LTBT treatment supervisor support for the DOH/Health facility/clinic, community and the patient forms one of the cornerstones of the DOTS strategy.

In a study treatment success rate of patients was 78% and 77% by DOTS from community volunteers and from government health workers respectively (Singh AA *et al,* 2004). Effectiveness of community volunteers in treating tuberculosis with DOTS, showed treatment success rate increased significantly from 13% in 2000 to 25% in 2002, even in absence of financial incentives (Singh AA *et al,* 2004).

The purpose of DOTS as a public health strategy is aimed at reducing the transmission rate of tuberculosis (Golub JE *et al,* 2006) and the likelihood of poor adherence to tuberculosis regimens (Bam TS *et al,* 2006, Juan G *et al,* 2006) that could lead to drug resistance (Anuradha B *et al,* 2006). The purpose of directly observed IPT is focused on adherence and the prevention of the development of active tuberculosis in high risk groups and thus indirectly reducing the tuberculosis transmission rate and tuberculosis drug resistance.

The cohort study in rural South Africa (Rowe KA *et al,* 2005) showed lamentably poor adherence to LTBT in rural South Africa among HIV-infected individuals. This study highlighted that LTBT was underpinned by a complex interaction between health services and the social, economic and cultural environment of the residential areas. An interesting finding of this study where all participants were HIV-infected only 47.1% had completed therapy, where only five had disclosed their HIV positive status to someone who was able to support them emotionally and financially.

# CHAPTER 3: METHODS

## 3.1 Study design

### 3.1.1 Setting of the study in the Western Cape

The study was conducted in three established hospital-based HIV clinics; based at Groote Schuur, Tygerberg and New Somerset Hospitals in Cape Town, South Africa. For much of the study period these clinics were the only public sector HIV outpatient facilities available and thus did not serve only as specialist referral centres.

### 3.1.2 Epidemiological study design

This study was based on a randomised double blinded clinical trial, with INH versus placebo administered on a twice weekly basis by patient nominated supervisors. The study commenced in early 1998 and was unblinded at the end of 2004.

## 3.2 Recruitment and selection of participants

### 3.2.1 Participant recruitment and selection

Clinicians in the three hospital-based adult HIV clinics in Cape Town, South Africa were requested to refer patients based on set criteria outlined in the memorandum. The three hospitals were Groote Schuur Hospital, Tygerberg Hospital and New Somerset Hospital. Memoranda were also circulated to various other hospitals and day clinics to refer patients who fulfilled the trial entry criteria.

### 3.2.2 Trial entry criteria

Inclusion and exclusion criteria targeted participants in WHO Clinical stage 3 or 4 stratified by TST status. The reasonable distance of the participants' residence to one of the three hospital based clinic trial sites was also taken into consideration before enrolling participants. More importantly, the screening process was designed to exclude participants with active tuberculosis (WHO Wkly Epidemiol Rec, 1999; Burgess AL *et al,* 2001; Aisu T *et al,* 1995; Espinal MA *et al,* 1995).

#### *3.2.2.1 Participant inclusion criteria*

Adults aged 18 years or older with confirmed HIV infection (WHO Clinical stage 3 or 4) were invited to participate were TST negative. All participants who consented to the study were required to nominate a treatment supervisor. Eligible participants were briefed about the trial in English, Afrikaans or Xhosa. Participants were requested to read and sign the consent form (Appendix 1). This signed informed consent form was obtained prior to participant screening for enrolment.

#### *3.2.2.2 Participant exclusion criteria*

Clinicians were asked not to refer patients with suspected tuberculosis or those with active tuberculosis. Exclusion criteria were one or more of the following; history of tuberculosis within the past five years (prior to date of enrolment), active alcohol abuse (based on clinicians report of clinical and patient history) or pregnancy (based on baseline questionnaire) or chronic liver disease (based on clinicians report of clinical and patient history), patients with a Karnofsky Performance score [KP<50 (Appendix 6)] and treatment with antiretroviral therapy [ART (which was not available in the South African public sector at the time of commencement of the study)]. Participants not residing within relatively easy reach of the IPT trial clinic sites were excluded from the trial.

Some participants accessed anti-retroviral therapy (ART) by enrolling in clinical trials that occurred sporadically during the study. Participants were censored at the time of initiation of ART.

The method of screening for tuberculosis (Mohammed A *et al*, 2004) excluding active tuberculosis prior to enrolment of participants to this IPT trial is described in detail in section 3.4 of this chapter. All participants underwent a screening symptom questionnaire, clinical examination, chest radiograph and sputum for smear and mycobacterial culture. Enrolment in the trial occurred four weeks after screening, when the sputum culture results were available.

The WHO clinical staging of all participants referred to the IPT trial was confirmed by clinicians based at one of the three hospital-based HIV clinics. The Karnofsky (KP) Scale Score of each participant was also noted to determine the participants' performance of activities of daily living. Participants with a Karnofsky score of less than 50 were not enrolled in the trial (Appendix 6). A KP Score ≥ 80 indicates the ability to carry on normal activities and to work with no special care required whereas a KP score between ≥ 50 and 70 indicates the inability to work but ability to live at home and care for most personal needs with varying amounts of assistance needed. A KP score of < 50 indicates an inability to care for oneself, i.e. where the disease may be progressing rapidly, requiring the equivalent of institutional or hospital care (Appendix 6).



### 3.2.3 Race classification of participants

The racial terms and race classification has been used in the context of South Africa's past legacy of Apartheid. Apartheid sought to categorise all South Africans into one of the four racial groups: Asian (or Indian) (2.6 percent of the population, 1996 census), African (or black) (76.7 percent), coloured (8.9 percent) and white (10.9 percent). The stratification by racial

group reflects enduring historical disparities in socioeconomic status, housing and access to medical care, and consequently in disease risk.

## 3.3 Tuberculin skin test (TST) and anergic tests

The Mantoux and Multipuncture tests to determine TST status and degree of anergy were performed on all participants that that granted written consent. The Mantoux and Multipuncture were done on the left and right mid forearm of all participants. The Mantoux test was performed on the same day as the Multitest® CMI Test (Pasteur Mérieux, Maidenhead, Berkshire, UK), according to the manufacturer's instructions and the administration of the structured questionnaire to the participants. Neither Mantoux nor the Multitest® CMI Test (Pasteur Mérieux) was conducted if the participants were excluded from the LTBT trial based on the entry criteria.

### 3.3.1 Mantoux test to determine TST status

The Mantoux test involved the intradermal injection of PPD on the area of the left mid forearm. These syringes filled with the required amount of PPD were ordered from the Pharmacy of Groote Schuur Hospital for each of the patients who were to be screened for the LTBT trial at all of the three hospitals, to ensure consistency and avoid possible loss of potency of the tuberculin (Marks J, 1964). The left arm of the participant was firmly supported by the nurse or relative or placed on the table, prior to intradermal injection. The intradermal injection area of the participant's mid forearm was cleaned with an alcohol swab (Appendix 7).

Once the area had dried, a tuberculin syringe and an intradermal needle (No 25G 16 mm long with a short bevel) was used to inject 0,1ml of PPD of 5 TU (American Lung Association, 1974) intradermally to produce a

wheal of about 5 mm diameter (Caplin, Maxwell, 1980). From its medial aspect the needle was introduced into the skin with the bevel facing upwards. Before injecting the PPD, the skin was gently elevated, so that the needle was advanced until the bevel was about 1 mm under the skin.

The Mantoux tests were read at 72 hours, by which time the area of the induration generally exceeds the area of the erythema (DHSS, Memorandum, 1972; Weston WL *et al,* 1976). On reading the Mantoux tests, the induration was first palpated with a finger and the edge of the diameter of the induration was marked both transversely and longitudinally, under good light with a ballpoint pen. The measurements were done with the aid of Vernier Callipers. The average of the transverse and the longitudinal diameter of induration in millimetres (Neville IK, 1957) was recorded as the final reading of the Mantoux tests for the respective patient.

A negative Mantoux test was interpreted at 72 hours as a PPD induration <5 mm. A patient with such a Mantoux result would be termed TST negative. A significantly positive Mantoux test (for HIV positive participants) was interpreted at 72 hours as PPD induration ≥5 mm. A patient with such a Mantoux result would be termed TST positive.



### 3.3.2 Multipuncture Test to assess degree of anergy

All participants referred for LTBT were assessed for anergy at the same time as the Mantoux Test. This measurement was performed by administering the Multitest® CMI Test (Pasteur Mérieux) on the participant's right mid forearm. The Multitest® CMI test is an acrylic resin applicator comprising of eight heads fixed to the base and loaded with seven different standard antigens and a glycerine control.

These seven antigens are tetanus, diphtheria, streptococcus, tuberculin, proteus, trychophytron and candida. The antigens on this applicator enable one to measure the degree of immunodeficiency and responses have been shown to correlate with the severity of HIV infection (Hersch EM *et al,* 1984a; Mathur-Wagh U *et al,* 1984; Hersch EM & Reuben JM, 1984b). The Walter Reed Army Institute in the US has used this method to determine the degree of response anergy as a means of classification of the stages of HIV infection (Redfield RR, 1986).

As in the case of the Mantoux test, the area of the right mid forearm was cleaned with alcohol and allowed to dry before applying the Multitest® CMI. This was removed from the refrigerator one hour before the tests to facilitate the removal of the caps from the antigen heads. Before the removal of the caps, the protective film covering of these caps was faced upwards and the bar of the Multitest® CMI was tapped on a hard surface. This was to ensure consistent impregnation of the antigens on the surface of the right mid forearm of the participant.

The Multitest® CMI was held on the T-bar; the protective film and antigen head caps were removed and the applicator was applied to the right mid forearm to enable the heads to make small punctures on the surface of the skin and release the antigens. This was achieved by maintaining a firm pressure on the surface of the arm for at least five seconds and then rocking the applicator from side to side and from top to bottom.

This enabled one to clearly see the circular impression on the participant's skin, where the skin perforations for each of the antigen heads resulted in the shining liquid (antigen) being impregnated in each of the square perforated areas on the right mid forearm.

The Multitest® CMI tests were read at 48 - 72 hours. As with the Mantoux test, the induration was measured with the aid of Vernier Callipers. The

average of the transverse and the longitudinal diameter of induration for each of the antigens were recorded in millimetres.

Positive results for individual antigens were defined by an induration size of 2 mm or more. A score for each participant was derived based on the sum of the average of all the positive reactions (indurations). From this score a compound score was calculated to determine the degree of anergy. The compound score was calculated based on the sum of all average positive indurations (≥2 mm) which was divided by the number of positive antigens (≥ 2mm).

The interpretation of Multitest® CMI tests for the degree of anergy of the participant was based on the calculation of the compound score. If these compound scores were below the manufacturer's cut-off points then the participant was confirmed as anergic. These cut-off scores were termed the alarm score. The alarm score for female patients was ≤5 mm and for male patients was ≤10 mm. Any value scored below these alarm scores was interpreted as anergic in accordance with the specifications of the manufacturers.



## 3.4 Screening of participants referred for IPT

### 3.4.1 Screening of participants

The screening of participants for the RCT involved the administration of the structured symptom questionnaire, chest radiography, sputum tuberculosis microscopy and tuberculosis culture, determining the participant's Karnofsky Score), patient's anergy and TST status, as well as various other tests (refer to section 3.5.5 of Methods chapter). A simple tuberculosis screening instrument was developed and used on participants

who had consented to partake in the trial prior to them being enrolled for IPT.

Once the referred eligible participants had given their written consent they were included to partake in the IPT trial. Enrolment occurred four weeks after screening of participants when the sputum culture result was made available.

### 3.4.2 Structured symptom questionnaire and patient record

The initial screening process involved the administration of a structured questionnaire (Appendix 2) to the potential participants by the nurse, at the initial interview, using a translated questionnaire with an option of the participant to have it administered in English, Afrikaans or Xhosa. The whole patient record consisted of four sections:

- Demographic and clinical data of the participants;
- Tuberculosis screening and baseline investigations;
- Monthly screening and monitoring of participants;
- Tuberculosis tests and cytometer readings for CD4 determination at 6 monthly intervals.



### 3.4.3 Chest radiography

A single investigator (GM) who was blinded to the laboratory diagnosis of tuberculosis assessed the chest radiographs prior to the patient being enrolled into the trial. The radiographs were interpreted as normal, abnormal but not suggestive of active tuberculosis, or abnormal compatible with tuberculosis (pulmonary infiltrates, adenopathy or pleural effusions).

### 3.4.4 Sputum tuberculosis microscopy and culture

One sputum sample was collected at the clinic visit if the patient was able to produce sputum. If the patient was unable to produce sputum at the clinic, a container was given to the participant to produce an early morning specimen. Sputum microscopy (auramine stain) and mycobacterial culture (radiometric Bactec® system) were performed in all patients. Participants returned after 4 weeks when the sputum culture result was available. Participants with non-tuberculosis mycobacteria were excluded from the study,

Tuberculosis was classified as definite (culture-positive together with appropriate symptoms or radiographic appearances), probable (smear-positive) and possible (clinical diagnosis together with a response to therapy). These definitions were also used to define cases of tuberculosis occurring after enrolment.



### 3.4.5 Other tests

Blood was collected to determine the baseline CD4+ lymphocyte count. At each clinic visit the following were assessed for each participant: symptoms of tuberculosis, adverse effects by symptom screening (i.e. rash hepatitis and neuropathy) and weight (measured with a beam balance scale zeroed at each session). The body temperature of the participant was also recorded and urinalysis (to detect bilirubinuria as a screen for hepatitis) was done. However, routine liver function tests were not done.

### 3.4.6 Use of TB screening instrument prior to initiating IPT

Previous studies have shown that tuberculosis was identified prior to treatment particularly in HIV testing centres in developing countries, as a result of active case findings where undetected cases were confirmed (Burgess AL, 2001; Aisu T *et al,* 1995; Espinal MA *et al,* 1995).

All participants (referred for this trial) who were screened for active tuberculosis were required to return to clinic after four weeks when the sputum culture and other various test results were available. The ability of symptoms, measured weight loss and radiographic abnormalities to predict active tuberculosis singly or in combination was assessed. Participants identified as having active tuberculosis based on one of the three definitions of active tuberculosis were excluded from the LTBT trial and referred to the clinic for tuberculosis treatment.

## 3.5 Randomization of participants enrolled for IPT

### 3.5.1 Sample size

The sample size was calculated using an estimated tuberculosis incidence of 30% per annum in the placebo control group, based on published data from HIV-infected patients with WHO clinical stage 3 and 4 (Pape JW *et al,* 1993) and an anticipated 80% reduction in tuberculosis incidence among TST-negative patients receiving INH compared to placebo. This estimated reduction was based on a study using INH for 12 months, which reported reductions in tuberculosis incidence of 71% on their whole population and 83% in TST positive participants (Pape JW *et al,* 1993). A one-tailed test significance tailed was done to detect tuberculosis risk in the intervention group since it was believed that this reasonable given what is known about IPT in the TST negative patients with advanced HIV disease.

Based on this premise, that patients with advanced disease had near-universal exposure to tuberculosis because of the very high prevalence of LTBI and the high tuberculosis incidence in our area (Rangaka MX *et al,* 2007). Given that TST is increasingly likely to become negative in advanced HIV disease, it was reasoned that although participants were TST negative they had LTBI. With Type-1 and -2 error proportions of 0.05 and 0.20 respectively and with a 1-tailed test, we estimated that 47

participants would be needed in each trial arm to be followed-up for 24 months.

### 3.5.2 Randomisation

Randomisation was conducted by a computer programme permuted in blocks of 20 with 1:1 ratio, to ensure that equal numbers of participants were selected between INH and placebo groups throughout the recruitment phase. Treatment allocation was kept in a sealed envelopes and the randomization code was passed on to an independent pharmacist who numbered the monthly INH/placebo packs appropriately. TST negative participants were assigned treatment numbers in numerical order at the time of enrolment. The participants with their unique number which matched the matching INH or placebo number, was maintained throughout the trial.

The blinding' of the RCT for participants researcher and clinicians was maintained till the analysis of the data was completed. An independent person held the sealed randomization code until the end of the study. TST positive participants (who were not randomised) were assigned to the open-label INH and underwent the same enrolment and follow-up schedule as trial participants.

TST negative participants in WHO Clinical stage 3 or 4 who qualified to be enrolled in the IPT trial were randomised to receive INH or matching placebo to be administered by a patient nominated supervisor (who had been briefed on his/her role as a supervisor). Participants in WHO Clinical stage 3 or 4 testing TST positive in the INH open-label arm were also required to nominate a treatment supervisor.

INH/placebo was administered for 12 months and all were followed for 24 months with six monthly sputum culture and chest radiography.

Participants in the trial did not have access to ART via the public health facilities at the time.

### 3.5.3 Participant nominated treatment supervisor for IPT trial

One of the major concerns raised in IPT, is non-adherence that could lead to INH resistance. In an attempt to reduce this risk of poor adherence (Ngamvithayapong, J *et al*, 1997; Aisu T *et al,* 1995; WHO Wkly Epidemiolo Rec, 1999; WHO/TB98.242; Calvacante S *et al* 1999), participants were required to nominate their treatment supervisors who would ensure the compliance of the intermittent INH and Pyridoxine during the period of the IPT trial. Both TST negative and positive participants were thus assigned to their nominated treatment supervisor to enhance participants' treatment adherence and to report any adverse effects of the trial medication.

These treatment supervisors were categorized into one of the following groups depending on their site: home, community or work. The home supervisors were defined as members residing in the home of the participant who may or may not be related to the participant. The community supervisors were defined as persons who were volunteers from community based organisations (CBOs), non-governmental organisation (NGOs), faith based organisations (FBOs) or community based organisations (CBOs) or neighbour, friend, or nurse at the clinic nearest to the participants' residence. The work supervisors were defined as people based at the participants' place of work. Treatment supervisors were asked to directly observe and administer the twice weekly doses of INH/placebo with Pyridoxine and to complete a monthly tick sheet of observed doses. The treatment supervisors were briefed on the need to ensure that support and encouragement were rendered to the participants for 12 months. Participants and their treatment supervisors were educated about early symptoms of adverse reactions, particularly hepatitis

(Comstock GW, 1986), and advised to report to the clinic immediately if these developed.

Participants were issued with a monthly clinic visiting card (Appendix 3), which in addition to indicating the scheduled dates of the monthly clinic visits of the participant, had an enforcing message on the need to be adherent and reiterating that tuberculosis was preventable, treatable and curable if medication was taken regularly as prescribed.

### 3.5.4 Trial medication and dosage

The TST negative participants were randomized to receive twice weekly INH (15 mg/kg/dose: 900 mg for those weighing 55 kg or more and 800 mg for those that weighed less than 55 kg) or matching placebo for 12 months. This dose was well tolerated and effective in a secondary prophylaxis trial in Zaire (Perriens JH *et al,* 1995); a primary prophylaxis trial in Haiti (Halsey NA *et al,* 1998) and in Zambia (Mwinga A *et al,* 1998). INH/placebo was stopped after 12 months or if participants had defaulted therapy for a period of 3 consecutive months. INH/placebo was discontinued permanently in participants defaulting for three or more consecutive months.

All participants were also supervised twice weekly with 25 mg Pyridoxine that was also administered and supervised by the treatment supervisor. All participants also received Cotrimoxazole 480 mg (Boeree MJ *et al,* 2005) daily as per clinic protocol. Cotrimoxazole was self-administered by the participants on a daily basis (without participant supervision). Adherence to INH/placebo, Pyridoxine and Cotrimoxazole was assessed by pill count at the participants' monthly clinic visit as well as on the monthly supervisor tick list report (Appendix 4) that was completed and by the treatment supervisor and submitted at their monthly clinic visit.

### 3.5.5 Intervention: Monthly evaluation of LTBT trial participants

A nurse and the study co-ordinator reviewed each participant monthly for the first 12 months (Comstock GW, 1999). Thereafter, participants were followed up at three monthly intervals for 12 months. At each clinic visit, the participants were assessed for symptoms of tuberculosis, adverse effects of INH and cotrimoxazole, weight, temperature and urinalysis (to detect bilirubinuria as a screen for hepatitis). Routine liver function tests were not done since hepatotoxicity was uncommon in prior studies (Wilkinson D, 2000, Agarwal SK, 2004). The same procedure was applied to the participants who were placed in the INH open-label arm.

A further 12 months of self administration of Cotrimoxazole was monitored and the participants were followed up at three monthly intervals for this period and referred to a clinician for clinical examination at six monthly intervals. Clinicians reviewed each participant at 6-monthly intervals. Chest radiographs and sputum (for smear and mycobacterial culture) were repeated every 6 months until month 24. If participants had features suggestive of tuberculosis before the 6-monthly visits, tests for tuberculosis were conducted as clinically indicated. CD4+lymphocyte counts were done every six months.

If participants were suspected to have tuberculosis during any of the monthly clinic visits prior to the six monthly clinician visit, chest radiographs, sputum (for smear and mycobacterial culture) were requested and participants were referred to the clinician for further clinical assessment and confirmation or exclusion of active tuberculosis. The same procedure was applied to the participants who were placed in the INH open-label arm. Attempts were made to trace patients missing two consecutive monthly clinic visits with a home visit. Participants who could not be traced after defaulting for three consecutive months were regarded as lost to follow-up.

### 3.5.6 Endpoints of the study

The primary endpoint of this study was the development of active tuberculosis based on the case definitions of tuberculosis was classified as definite tuberculosis (culture-positive together with appropriate symptoms or radiographic appearances), probable tuberculosis (smear-positive) and possible tuberculosis (clinical diagnosis together with a response to therapy). The secondary endpoints were death, hospitalisation, adherence, change in CD4+ lymphocyte counts and adverse drug effects.

### 3.5.7 Data analysis

The confirmation of a TB culture was used as the 'gold standard' for a confirmed TB case. The test validity characteristics against the 'gold standard' of the screening instrument for diagnosing active TB in HIV-infected adults with advanced disease were calculated with their 95% confidence intervals. A logistic regression model was used to assess the independent predictive effects in identifying active tuberculosis of the 'different tests'.



Data were analyzed using the statistical programme SAS Version 9.0 (SAS Institute, Cary, NC, USA). All trial analyses were by intention-to-treat. The distribution of predictors of tuberculosis risk at baseline was assessed using the Student's t-tests, Wilcoxon rank-sum tests, and Fisher's exact tests, as appropriate.

The effect of INH versus placebo on the rate of tuberculosis disease was based on person-time calculated from the date of randomization into the trial until the earliest of three endpoints: documented tuberculosis disease, censoring (due to loss to follow-up, initiation of ART or death due to other opportunistic infections), or the end of the study in December 2004, when all participants had completed 24 months of follow-up. Kaplan-Meier analyses were used to calculate tuberculosis-free survival probabilities and survival

curves were compared using log-rank tests. Cox's proportional hazards analyses were used to examine the effect of treatment on the rate of tuberculosis disease after adjusting for minor imbalances in baseline covariates.

Adherence was analysed by pill count as the percentage of doses taken by the participants over a period of 12 months at intervals of four weeks, over the percentage prescribed doses.

## 3.6 Ethical issues

The study was approved by the Ethics and Research Committees (Appendix 5) of the Universities of Cape Town and Stellenbosch. Signed informed consent was obtained from each participant prior to screening and prior to enrolment into the LTBT trial.

The participants were briefed about the trial in English, Afrikaans or Xhosa. Once verbal consent was obtained the participant was requested to read and sign the consent form in the language of their choice before initiating the screening process with the aim of enrolling eligible participants into the trial.

Participants whose TST status was positive were excluded from the randomised LTBT trial but were given the option of joining the open label INH arm. This was done on purely ethical grounds, since studies had already established the benefit of LTBT among HIV-infected individual who are TST positive (Woldehanna S & Volmink J 2004; Bucher HL *et al,* 1999). These TST positive participants in the open label INH arm were followed up in the same manner as the TST negative participants who were enrolled in the closed label INH/placebo arm.

Participants were required to nominate treatment supervisors who were aware of the participants' HIV status and those treatment supervisors were informed about the importance of maintaining confidentiality. If the participant did not wish to have their HIV status divulged to the treatment supervisor, confidentiality was assured to the participant and their treatment supervisors were informed that the trial was being undertaken to prevent tuberculosis in the participant who was being supervised.

All participants who were identified with active tuberculosis during the screening process or developed tuberculosis whilst on the IPT trial were referred to the nearest clinic for tuberculosis treatment. On enrolment and at the time of signing the consent form (Appendix 1), participants were once again reminded that their participation in the IPT trial was voluntary and that they had the right to withdraw from the trial at any time if they so wished.

All Participants were also advised of the possibility of adverse effects due to Cotrimoxazole, and that if such a reaction occurred, this antibiotic would be discontinued and replaced with another antibiotic. In the rare event of serious adverse effects due to INH, participants were informed that they would be taken off the IPT trial. Such adverse effects were defined as new skin rash, itchiness, pins & needles, numbness of the limbs and nausea).

Participants who had enrolled for the IPT trial were served with tea, coffee or soup during their monthly clinic visit while waiting to be assessed.

# CHAPTER 4: RESULTS

## 4.1 Background of participants for IPT trial

### 4.1.1 Recruitment and enrolment of participants for IPT trial

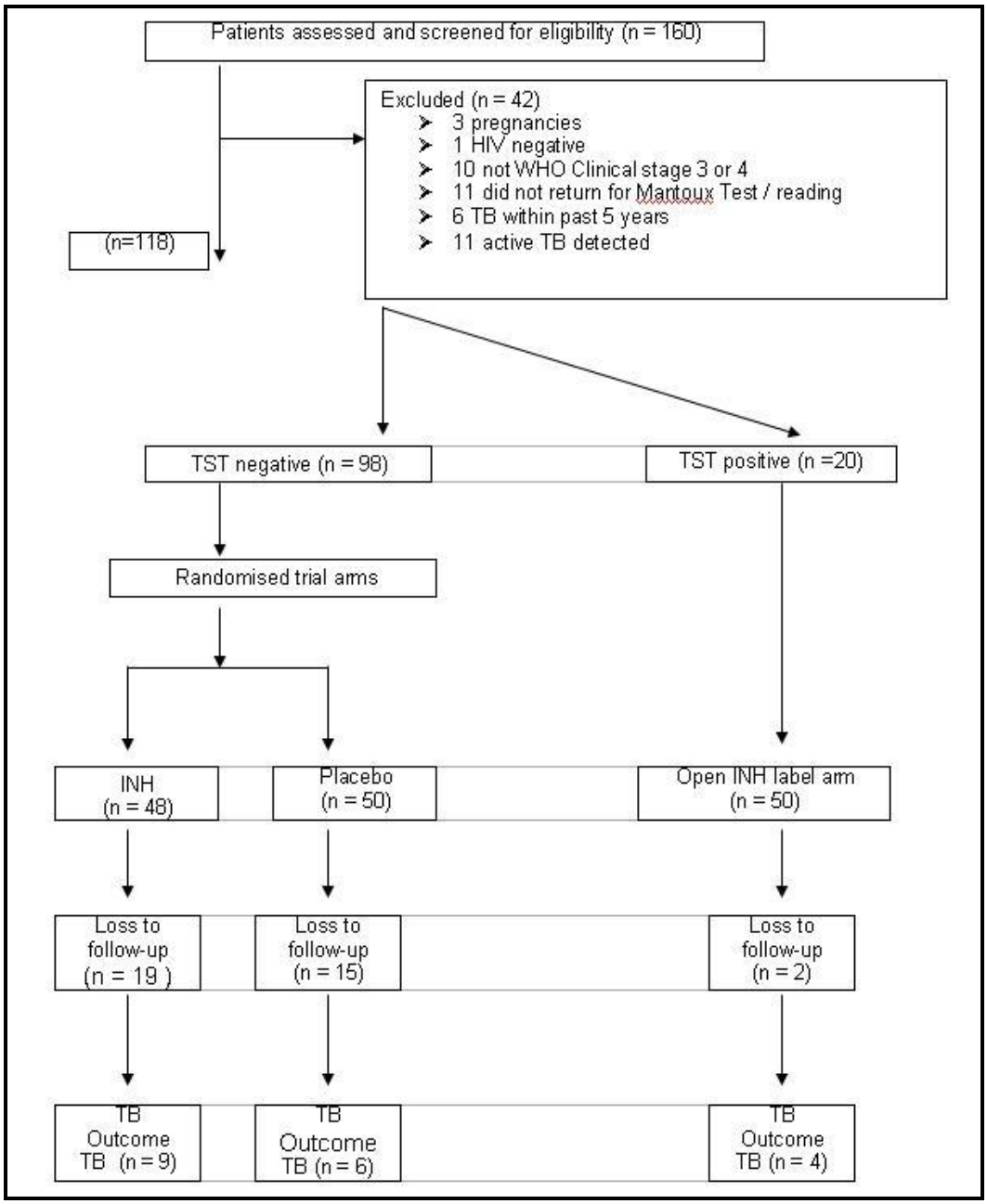
A total of 160 participants were referred for enrolment in the IPT trial. Figure 1, which presents the outcome of the 160 participants; the number of participants excluded prior to screening, the number of participants excluded upon screening and those participants on the LTBT trial who were observed for the period of 24 months.

Of these 160 individuals, 31 (19.4%) were excluded from enrolment which resulted in 129 (80.6%) individuals being screened for tuberculosis prior to the enrolment as recommended by WHO to prevent drug resistance (WHO, 1999). Of this group of 129 participants, an additional 11 (8.5%) participants were excluded based on the screening tests and the outcome of confirmatory tests confirming active tuberculosis status (Mohammed A *et al,* 2004), resulting in 118 eligible participants enrolled for the LTBT trial of which 20 (12.5%) participants were TST positive.

The 20 TST positive participants enrolled for the trial were not randomised in the double blind IPT trial, owing to the confirmation of their TST positive status, based on the Mantoux test. However, these 20 TST positive participants were placed in the open-label arm and administered INH. Both the 98 (83%) TST negative participants in the randomized trial arms (INH/placebo closed label arms) and the 20 (17%) TST positive participants in the open-label arm were treated and followed up in the same manner for the duration of this study.

The majority of the 64 (54.2%) participants enrolled for the LTBT trial were based at Groote Schuur Hospital, with 42 (35.6%) participants based at the New Somerset Hospital and 12 (10.2%) participants based at Tygerberg Hospital.

**Figure 1: Flowchart indicating progress of patients in the study**



### 4.1.2 Participants enrolled for IPT in the Trial

In the following section outlines the characteristics of all participants in the randomised arms as well as the open-label arm (INH).

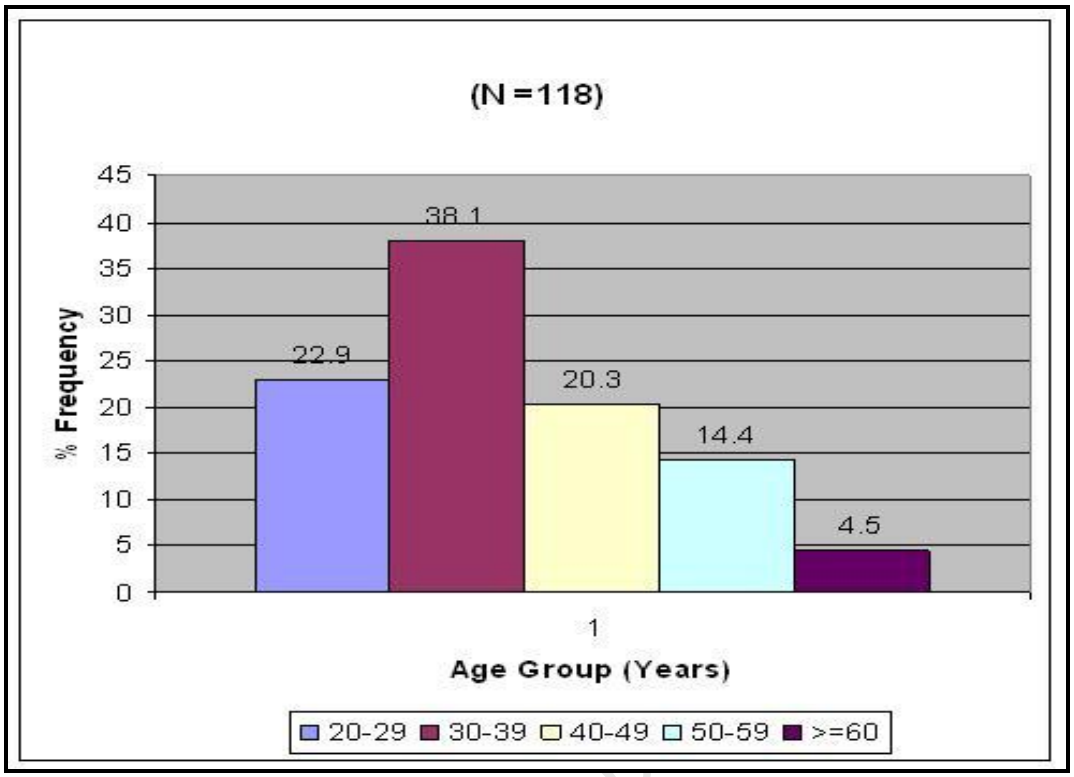
#### *4.1.2.1 Race, gender, sexual orientation and religion.*

The race distribution (refer to preceding paragraph for explanation of the use of race classification) of the 118 participants in both the closed and open INH label arms was 82 (69.5%) Blacks, 29 (24.6%) Coloureds, 3 (2.5%) Indians and 4 (3.4%) Whites. The race distribution of participants in the closed INH label comprised 66 (67.7%) Blacks, 25 (25.5%) Coloureds, 3(3.1%) Indians and 4 (4.1%) Whites.

Graph 1 displays the age distribution of this group. The mean age was 38.3 years with a standard deviation of 10.9 (range of 20 to 70 years). The gender distribution of the 118 participants was 63 (53.4%) females and 55 (46.6%) males. The religious distribution of participants in the closed and open INH label were 109 (92.4%) Christians and 9 (7.6%) Muslim. A total of the 113 (95.8%) participants were reported to be heterosexual, 2 (1.7%) bisexual and 3 (2.5%) homosexual.

The main mode of HIV transmission was thus by heterosexual means. However, among the 113 participants who reported a heterosexual orientation, one participant had reported HIV infection via blood transfusion and another participant reported HIV transmission as a result of rape. None of the participants had reported HIV transmission via intravenous drug use.

**Graph 1: Age distribution of participants**




### *4.1.2.2 Residential area of participants*

An overwhelming majority of the participants enrolled for the IPT trial were from lower socio-economic residential areas (historically disadvantaged townships), in Cape Town. The majority of the participants [62 (52.5%)] resided in Khayelitsha, Guguletu, Nyanga, Crossroads and Langa, previously designated Black townships; as well as predominantly Black informal settlements such as Brown's Farm, Philippi, Blue Downs, Mandalay and Milnerton. All of these residential areas, with an exception of two, were easily accessible to the Tygerberg, Groote Schuur and New Somerset Hospitals. An exception was made for two participants from distant areas, based on assurance of their regular clinic visits for the duration of the IPT trial. The clinic in Grabouw arranged transport for one participant's monthly visit to Tygerberg Hospital for the duration of the LTBT trial. The second participant from Atlantis commuted to Cape Town at least twice monthly. Assurance was given that this routine visit would be

arranged to coincide with her monthly visit to Groote Schuur Hospital for the duration of the IPT trial.

#### *4.1.2.3 Marital, educational, occupational status*

The marital, educational and occupational status of participants enrolled on the LTBT trial is presented in Tables 3, 4 and 5. Only 28 (23.7%) of the participants enrolled for IPT were married, as compared to the nine participants that reported having a common law spouse. The majority of the 81 (76.3%) participants enrolled on this trial were without a partner; single, separated, divorced or widowed. Most of the 63 (53.4%) participants reported being single.

**Table 3: Marital status of participants**

| **Marital Status** | **% Frequency** |
|---|---|
| Married | 28 (23.7%) |
| Divorced | 6 (5.1%) |
| Separated | 6 (5.1%) |
| Widowed | 6 (5.1%) |
| Common Law Spouse | 9 (7.6%) |
| Single | 63 (53.4% |
| **Total** | 118 (100%) |

Only three participants reported no schooling (Table 4) and 18 participants reported having received tertiary education. Of these 18 participants who received tertiary education, one had completed a Masters degree in theology and another had registered for a Masters degree in education.

**Table 4: Educational status of participants**

| Level of Education | % Frequency |
|---|---|
| Primary Schooling | 42 (35.6%) |
| Secondary Schooling | 57 (48.3%) |
| Tertiary Education | 16 (13.6%) |
| No Schooling | 3 (2.5%) |
| **Total** | 118 (100%) |

A total of 59 of the participants were unemployed (Table 5). Only 44 participants were employed. The other 15 participants were either in the category of pensioner, student, housewife, or had been medically retired. Of the 44 (37.3%) participants who were employed, 35 participants were permanently employed, five temporarily employed and one employed on a part-time basis. Three participants did not respond to the question regarding their employment status.



**Table 5: Occupational status of participants**

| Occupational Status | % Frequency |
|---|---|
| Employed | 44 (37.3%) |
| Unemployed | 59 (50.0%) |
| Pensioner | 3 (2.5%) |
| Housewife | 1 (0.8%) |
| Student | 8 (6.8%) |
| Other | 3 (2.5%) |
| **Total** | 118 (100%) |

### *4.1.2.4 Distribution of social class*

Table 6 outlines the 118 participants placed into social class categories based on criteria established by the South African Labour Development

Research Unit (SALDRU, 1983). There were 67 participants who were placed in the 'partially or unskilled' social class category based on their current or previous work and designated position at workplace.

**Table 6: Social class category of participants**

| Category | Social Class | % Frequency (n = 118) |
|---|---|---|
| I | Professional | 1 (0.8%) |
| II | Intermediate | 3 (2.5%) |
| IIIa | Skilled Non-Manual | 19 (16.1%) |
| IIIb | Skilled Manual | 28 (23.7%) |
| IV | Partially Skilled | 49 (41.5%) |
| V | Unskilled | 18 (15.3%) |

The monthly income .ranged between from <R500.00 to ≥R3000.00 with 72 (61%) participants' income ranging between < R500.00 and R1499.00 per month.

**Table 7: Income category of participants**

| Category (Income per month) | Frequency | % Frequency |
|---|---|---|
| < R500.00 | 24 | 20.3 |
| R500.00 – R999.00 | 22 | 18.6 |
| R1,000.00 – R1,499.00 | 26 | 22.0 |
| R1,500.00 – R1,999.00 | 4 | 3.4 |
| R2,000.00 – R2,499.00 | 4 | 3.4 |
| R2,500.00 – R2,999.00 | 1 | 0.8 |
| ≥ R3000.00 | 5 | 4.2 |
| Dependent on family/external support | 32 | 27.1 |
| **Total** | 118 | 100.0 |

From Table 7, 44 participants reported being sole supporters of family or providers of household income. Seventeen participants reported that they did not or were not able to contribute at all to the family or household income.

Table 8 illustrates the supporting role of a family or a household member to the participant enrolled in the trial.

**Table 8: Participants supporting role in family or household**

| Category | Frequency | % Frequency |
|---|---|---|
| Sole supporter of family / household | 44 | 37.3 |
| Not sole supporter of family / household | 57 | 48.3 |
| Not contributing of support to household | 17 | 14.4 |
| **Total** | 118 | 100.0 |



## 4.1.3 Participants' sexual behaviour and practice in relation to HIV

### *4.1.3.1 Number of sexual partners and condom use of participants*

There were 72 (61%) participants who reported no sexual partners within the 6 months prior to enrolment. A total of 40 (33.9%) participants had reported having one sexual partner within the six months prior to enrolment; 4 (3.4%) participants reported two sexual partners; with only 2 (1.7%) participants reported having had three or more sexual partners within the 6 months prior to enrolment.

Table 9 presents the responses regarding participants' use of condoms. There were 57 participants who reported that they abstained from sex. Of the 61 participants who reported being sexually active, there were 27 who

reported using condoms every time as compared to 12 participants who used condoms sometimes and 22 participants who never used condoms.

**Table 9: Participants' use of condoms**

| Condom Use | % Frequency |
|---|---|
| Abstained from sex | 57 (48.3%) |
| Always use condom | 27 (22.9%) |
| Sometimes | 12 (10.3%) |
| Never | 22 (18.6%) |
| **Total** | 118 (100%) |

#### *4.1.3.2 Partners' awareness of participants' HIV status*

A total of 63 (53.4%) participants reported that their partners were aware of their HIV positive status, as compared to 41 (34.7%) participants who had partners who did not know of their HIV positive status. Only 14 (11.9%) participants reported that they did not know if their partner knew of their HIV positive status.

### 4.1.4 History of TB and household tuberculosis contacts

#### *4.1.4.1 History of TB five years prior to enrolment for IPT Trial*

The criteria aimed to exclude participants who had a history of tuberculosis within five years prior to enrolment. However, 18 (15.3%) participants who reported history of tuberculosis more than five years previously were eligible to be enrolled. Twenty seven (22.9%) participants reported having had a household member who had been diagnosed with and treated for tuberculosis. Six (5.1%) participants did not know if they had ever been in contact with a household member with tuberculosis.

#### *4.1.4.2 Participants' history of BCG and BCG scar*

The relationship between participants' reports of having received BCG and the presence of the BCG scar was checked on enrolment. Table 10 illustrates the relation between reported BCG and the observed BCG scar No BCG scar was observed among 43 (54.4%) of the 79 participants who reported having received BCG. However, among the 37 participants with a BCG scar, 36 (97.3%) participants had reported that they had received BCG. Thus only one (0.8%) participant with a BCG scar reported no recollection of having received BCG. In 18 (15.3%) participants there was agreement between absence of a BCG scar and a report of not having received BCG vaccination.

**Table 10: Relationship between reported BCG and observed BCG scar**

| | **Reported to have received BCG vaccination** | | | |
|---|---|---|---|---|
| **BCG scar observed** | **Yes** | **No** | **Don't Know** | **Total** |
| **Yes** | 36 | 0 | 1 | 37 |
| **No** | 43 | 18 | 20 | 81 |
| **Total** | 79 | 18 | 21 | 118 |



### 4.1.5 Tuberculin skin test (TST)

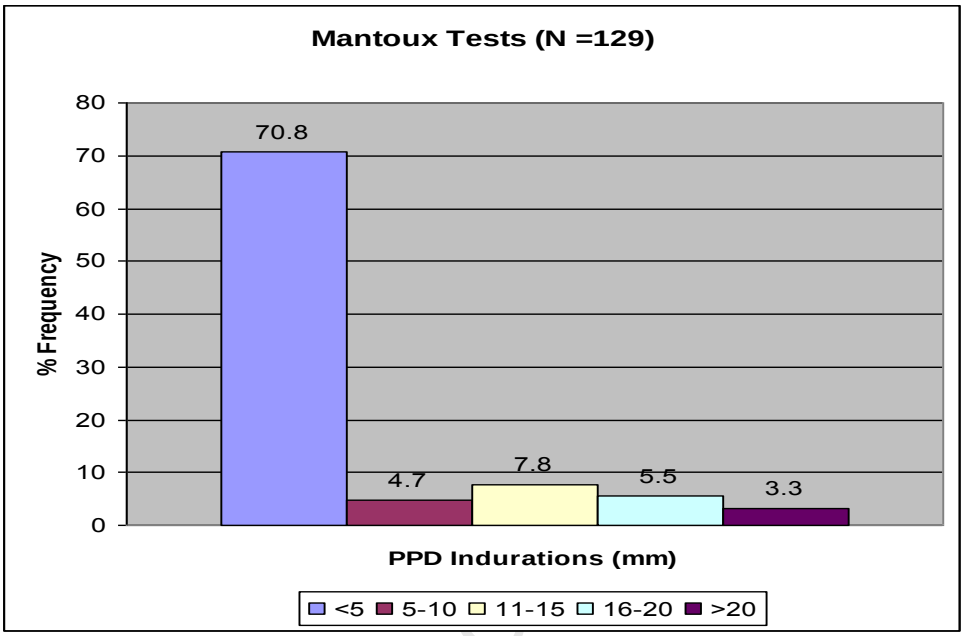
Two types of skin tests were performed on all participants. The Mantoux test was performed to ascertain the TST status of the participant, whereas the Multipuncture Test (Multitest® CMI) conducted at the same time assessed the degree of anergy of the participants.

#### *4.1.5.1 Mantoux test*

Of the 129 individuals tested with Mantoux test, 26 (20.2%) were TST positive and of the 26 TST positive participants, six (23.1%) participants were confirmed as having active tuberculosis at enrolment based on the tuberculosis screening instrument (see section 2 of the Results chapter).

Of the 103 TST negative participants, five (4.8%) were confirmed with tuberculosis based on the screening instrument.

**Graph 2: Participants screened by Mantoux test**




Thus eleven (8.5%) participants were excluded (because of active tuberculosis) from the IPT trial and were referred to the clinic nearest to their residence for tuberculosis treatment. Graph 2 shows the distribution of the results of the Mantoux test of the 118 (98 TST negative and 20 TST positive) enrolled for the IPT trial



### *4.1.5.2 Multipuncture test result (Multitest® CMI)*

In Table 11, all of the 26 (20.2%) TST positive participants (both male and female) had a compound score (refer to section 3.4.2 of Methods chapter) exceeding the alarm score, indicating that this group did not display a high degree of anergy. However, the 103 (79.8%) participants in the TST (PPD) negative cohort (both male and female) all had a compound score of zero and well below the alarm score indicating that the participants in this cohort had a high degree of anergy.

**Table 11: Participants screened (Multitest® CMI) for level of anergy.**

| Patient ID | Sex | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Score | Compound Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 301 | F | 0 | 0 | 0 | 11.5 | 0 | 0 | 0 | 0 | 11.5 | 11.5 |
| 302 | F | 0 | 0 | 0 | 10.0 | 0 | 0 | 0 | 0 | 10.0 | 10.0 |
| 303 | F | 0 | 0 | 0 | 10.0 | 0 | 0 | 0 | 0 | 10.0 | 10.0 |
| 304 | F | 0 | 0 | 0 | 11.8 | 0 | 0 | 0 | 0 | 11.8 | 11.8 |
| 305 | M | 0 | 0 | 0 | 10.2 | 0 | 0 | 0 | 0 | 10.2 | 10.2 |
| 306 | M | 0 | 0 | 0 | 10.1 | 0 | 0 | 0 | 0 | 10.1 | 10.1 |
| 307 | M | 0 | 0 | 0 | 13.8 | 0 | 0 | 0 | 0 | 13.8 | 13.8 |
| 308 | F | 0 | 0 | 0 | 10.2 | 0 | 0 | 0 | 0 | 10.2 | 10.2 |
| 310 | F | 0 | 0 | 0 | 8.0 | 0 | 0 | 0 | 0 | 8.0 | 8.0 |
| 311 | M | 0 | 0 | 0 | 10.5 | 0 | 0 | 0 | 0 | 10.5 | 10.5 |
| 312 | F | 0 | 0 | 0 | 10.5 | 0 | 0 | 0 | 0 | 10.5 | 10.5 |
| 313 | M | 0 | 0 | 0 | 12.0 | 0 | 0 | 0 | 0 | 12.0 | 12.0 |
| 314 | F | 0 | 0 | 0 | 14.0 | 0 | 0 | 0 | 0 | 14.0 | 14.0 |
| 315 | F | 0 | 0 | 0 | 8.0 | 0 | 0 | 0 | 0 | 8.0 | 8.0 |
| 316 | M | 0 | 0 | 0 | 10.1 | 0 | 0 | 0 | 0 | 8.0 | 8.0 |
| 317 | F | 0 | 0 | 0 | 6.0 | 0 | 0 | 0 | 0 | 10.1 | 10.1 |
| 318 | M | 0 | 0 | 0 | 10.2 | 0 | 0 | 0 | 0 | 6.0 | 6.0 |
| 319 | F | 0 | 0 | 0 | 8.0 | 0 | 0 | 0 | 0 | 10.2 | 10.2 |
| 320 | F | 0 | 0 | 0 | 7.0 | 0 | 0 | 0 | 0 | 8.0 | 8.0 |
| 321 | M | 0 | 0 | 0 | 11.0 | 0 | 0 | 0 | 0 | 7.0 | 7.0 |
| X1 | F | 0 | 0 | 0 | 5.2 | 0 | 0 | 0 | 0 | 5.2 | 5.2 |
| X3 | M | 0 | 0 | 0 | 10.1 | 0 | 0 | 0 | 0 | 10.1 | 10.1 |
| X6 | M | 0 | 0 | 0 | 10.2 | 0 | 0 | 0 | 0 | 10.2 | 10.2 |
| X10 | M | 0 | 0 | 0 | 10.5 | 0 | 0 | 0 | 0 | 10.5 | 10.5 |
| X11 | F | 0 | 0 | 0 | 5.3 | 0 | 0 | 0 | 0 | 5.3 | 5.3 |
| X31 | F | 0 | 0 | 0 | 8.3 | 0 | 0 | 0 | 0 | 8.3 | 8.3 |

Key to Antigens: 1 = tetanus; 2 = diphtheria; 3 = streptococcus; 4 = tuberculin; 5 = glycerine; 6 = candida; 7 = trichophoton; 8 = proteus

## 4.6 Tuberculosis screening

All individuals who consented to participating in the IPT trial were microbiologically tested for active tuberculosis prior to enrolment to the IPT trial. The following section outlines the level of performance of the tuberculosis screening instrument among the 129 individuals that had indicated their willingness to participate in the trial.

### 4.6.1 Tuberculosis screening instrument performance

One hundred and twenty nine patients were screened for tuberculosis. tuberculosis was diagnosed in 11 (8.5%) patients ten definite and one possible (fever and meningitis with cerebrospinal fluid negative for cryptococcal antigen and negative cultures for bacteria, fungi and mycobacteria and a good response to anti- tuberculosis therapy).

The performance of the individual screening elements for these 11 cases of tuberculosis is shown in Table 12. A screening instrument defined as two or more signs/symptoms of measured weight loss, cough, night sweats or fever had a sensitivity of 100% [(lower 95% confidence interval (CI): 67.9)] and specificity of 88.1% (95% CI 80.6 – 93.1). In logistic regression analysis, these four variables were all independent predictors of tuberculosis. The positive and negative predictive values of this screening instrument were 44% and 100% respectively (likelihood ratio positive 8.43). In logistic regression modelling this screening instrument provided the best fit (Wald statistic 19.64, $p < 0.001$).

Adding the Mantoux or chest radiograph result did not improve the performance of the screening instrument. If only one of the four variables was used for screening, the specificity was reduced to 53.4% (95% CI 44–62.5). The sensitivity and specificity of any three of the four variables

(weight loss, cough, night sweats or fever) were 82% and 97% respectively; and for all four were 27% and 100%, respectively.

**Table 12: Performance of individual tuberculosis screening elements in HIV WHO Clinical Stage 3 or 4 patients**

| Screening Test | Sensitivity | Specificity | Odds ratio (95% CI)* | P** |
|---|---|---|---|---|
| Observed weight loss ≥ 2.5% in 4 weeks | 81.8% | 78.8% | 12.6 (2.9-55.3) | < 0.01 |
| Cough > 2 weeks | 81.8% | 88.1% | 20.7 (4.8-89.7) | < 0.01 |
| Night Sweats > 2 weeks | 72.7% | 88.1% | 12.9 (3.7-45.1) | < 0.01 |
| Fever > 2 weeks | 72.7% | 83.1% | 9.6 (2.7-33.9) | < 0.01 |
| Mantoux ≥ 5 mm induration | 54.5% | 83.1% | 4.8 (1.6-14.4) | 0.01 |
| Chest X-ray suggestive | 27.3% | 95.8% | 5.7 (1.9-17.3) | 0.02 |
| Sputum smear positive | 54.5% | 100% | N/A | N/A |
| Sputum culture positive | 90.9% | 100% | N/A | N/A |

* Odds ratios of association between symptom & active tuberculosis adjusted in logistic regression;

** Fishers exact 2-tailed test



### 4.6.2 Chest radiographs, sputum tuberculosis microscopy and culture

Table 13 illustrates that in accordance with trial protocol, chest radiographs, sputum microscopy and culture for tuberculosis were conducted at 6-monthly intervals for 24 months, with assessment by clinicians.

Of the 6-monthly tests conducted; 198 (68.3%) of the 290 required chest radiographs were done with 7 (3.5%) suggestive of tuberculosis; 197 (65.7%) of the 300 required sputum microscopy were done of which three (1.5%) were smear positive; and 193 of the 294 (65.6%) required sputum cultures were done of which 6 (3.1%) were culture positive for tuberculosis. Follow-up and outcome data are listed in Table 13. Of the 15 participants in the randomised trial arms diagnosed with tuberculosis, 6 (40%) were detected during routine clinic visits (two possible; one probable and three definite tuberculosis).

**Table 13: Six-monthly tests of chest radiographs, microscopy and culture over a period of 24 months**

| Type of Tests | Total number (n) done | Total number (N) required | % done |
|---|---|---|---|
| Chest Radiographs | 198 [7 (3.5%)TB suggestive] | 290 | 68.3% |
| Microscopy | 197 [3 (1.5%) smear positive] | 300 | 65.7% |
| Culture* | 193 [6 (3.1%) culture positive] | 294 | 65.6% |

* Remaining four tuberculosis cases were detected on signs & symptoms alone



### 4.6.3 Karnofsky performance scale score

Table 14 presents the assessment of the Karnofsky Performance Scale Score (KP) of all participants prior to enrolment to LTBT. The Karnorfsky Performances Scale Score allows one to classify the participants' functional impairment into three broad categories. Only 14 of the participants had a Karnofsky Performance Scale Score of < 70.

**Table 14: Karnofsky Performance Score for TST +ve & -ve participants**

| Karnofsky Score | PPD-ve | PPD+ve | Total |
|---|---|---|---|
| 50 | 2 (2.0%) | ---- | 2 (1.7%) |
| 60 | 11 (11.2%) | 1 (5.0%) | 12 (10.2%) |
| 70 | 35 (35.7%) | 2 (10.0%) | 37 (31.4%) |
| 80 | 21 (21.4%) | 7 (35%) | 28 (23.7%) |
| 90 | 29 (29.6%) | 10 (50.0%) | 39 (33.1%) |
| **Total** | 98 (83.1%) | 20 (16.9%) | 118 (100%) |

There was significantly statistical association between participants with a Karnofsky Score ≤ 70 and a TST negative status with a OR 5.44 [95% CI: 1.50 -19.76 (Table 15)],

**Table 15: Association between Karnofsky Score and TST Status**

| Karnofsky Score | PPD-ve | PPD+ve | Total |
|---|---|---|---|
| ≤ 70 | 48 | 3 | 51 |
| > 70 | 50 | 17 | 67 |
| Total | 98 | 20 | 118 |



### 4.6.4 Baseline characteristics, clinical features & laboratory results of enrolled participants

As can be seen from Table 16, the baseline characteristics of demographics, clinical features and laboratory results of the enrolled participants in the randomised trial arms were well matched. However, the TST positive participants had less severe HIV disease in comparison to the randomised trial arms, as assessed by the higher Karnofsky score (p = 0.013), higher CD4 count (p = 0.001) and lower proportion with WHO Clinical stage 4 (p = 0.001).

**Table 16: Baseline comparison of study arms**

| | **Randomized Arms** | | | **INH Open** |
|---|---|---|---|---|
| **Sample size** | INH (n=48) | Placebo (n=50) | p-value* for difference | Label Arm. (n=20) |
| **Demographics** | | | | |
| Mean age in years | 39.7 | 37.8 | 0.38 | 35.9 |
| Male | 25 (52%) | 22 (44%) | 0.54 | 11 (55%) |
| Race (African)** | 33 (69%) | 39 (78%) | 0.29 | 10 (50%) |
| Unemployed | 21 (44%) | 26 (52%) | 0.43 | 6 (30%) |
| ≥ Secondary Education | 31 (65%) | 30 (60%) | 0.68 | 11 (55%) |
| Social Class<br>Classes I - III<br>Classes IV - V | <br>22(46%)<br>26 (54%) | <br>22(46%)<br>28(56%) | 0.99 | <br>13 (65%)<br>7(35%) |
| Patient nominated supervisors:<br>Home-based<br>Community-based<br>Work-based | <br>36 (72%)<br>7 (14%)<br>7 (14%) | <br>31 (65%)<br>11 (23%)<br>6 (12%) | 0.52 | <br>12 (60%)<br>5 (23%)<br>3 (15%) |
| **Clinical features** | | | | |
| Mean Body Mass Index (BMI) | 23.1 | 23.5 | 0.68 | 23.8 |
| Previous TB diagnosis | 5 (10%) | 10 (20%) | 0.26 | 2 (10%) |
| Household contact with TB | 8 (17%) | 15 (30%) | 0.15 | 6 (30%) |
| WHO stage 4 | 22 (46%) | 23 (50%) | 0.99 | 1 (5%) |
| Median Karnofsky Score (IQR) | 80 (70-90) | 75 (70-88) | 0.62 | 85 |
| **Laboratory results** | | | | |
| Median CD4 (µL) count (IQR) | 99 (24-269) | 117 (56-236) | 0.55 | 354 (191-466) |

* It is between the randomised arms (INH & Placebo)

** Refer to section 4.1.2 of Results chapter

## 4.7 Follow-up and outcomes

The section deals with follow-up and outcomes in respect of tuberculosis between the treatment and control arms (INH and placebo closed–label arms) over the period of 24 months.

### 4.7.1 Person years of observation

Total person-years of observation in the trial was 160.4 person-years.

There was no difference in the total person-years of observation between randomised participants of the INH group (50.09 per person-years) and the placebo group (51.80 person-years). Among the open label INH group the period of observation was 58.25 person-years.

No statistically significant differences between participants in the randomized trial arms with regards to adherence, follow-up observation, hospitalization, CD4+ lymphocyte count decline, tuberculosis and death were observed (Table 17).

**Table 17: Follow-up and outcomes**

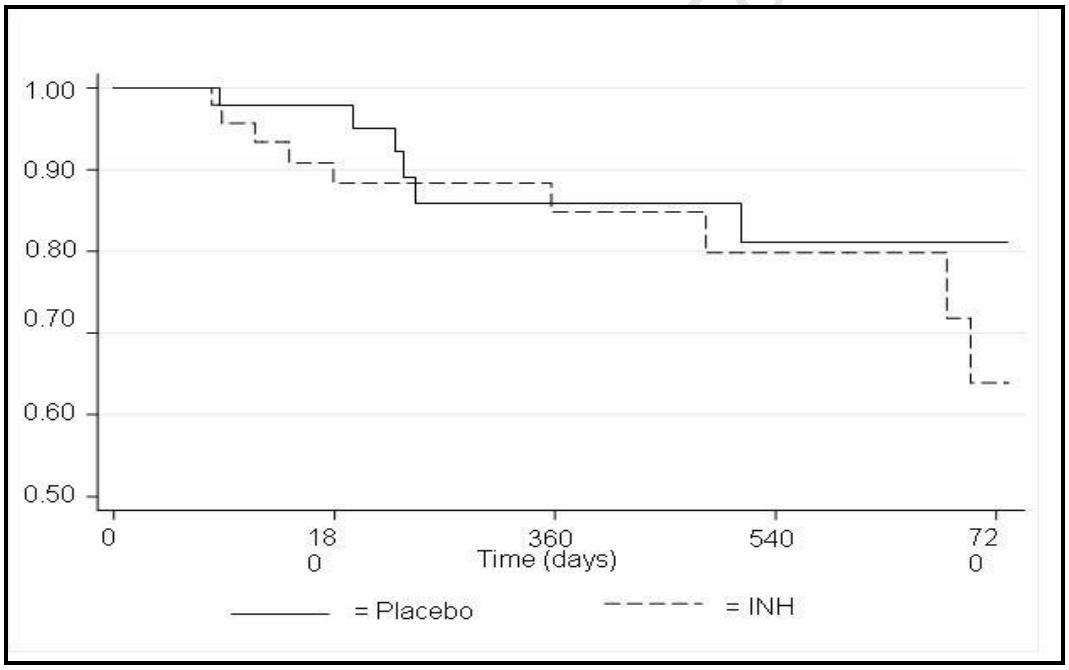
| | **Randomized Arms** | | | **INH Open** |
|---|---|---|---|---|
| **Sample size** | INH (n=48) | Placebo (n=50) | p-value | Label (n=20) |
| Median duration of follow-up (days) IQR | 350 (161 to 1592) | 358 (151 to 721) | N/A | 1130 (381 to1581) |
| Median % of doses taken IQR* | 87 (68 to 93) | 81.2 (70 to 90) | 0.11 | 91.7 (82 to 96) |
| Median change in CD4 µL count at 12 months follow-up IQR | -28 (-201 to 692) | -32 (-234 to 239) | 0.31 | -15 (-294 to 240) |
| Hospitalized during 24 months follow-up period | 45.9 per 100 p-y** | 46.3 per 100 p-y | 0.99 | 12.0 per 100 p-y |
| Censored: Initiating ARV therapy Lost to follow-up | 19 6 13 | 15 5 10 | 0.31 0.71 0.50 | 2 0 2 |
| Death (All cause) | 14 | 18 | 0.32 | 0 |
| Tuberculosis | 9 | 6 | 0.42 | 4 |
| Person years of observation | 50.09 | 51.80 | 0.76 | 58.25 |
| TB incidence (by any definition) | 18.0 per 100p-y (95% CI:8.2-34.1) | 11.6 per 100p-y (95% CI 4.2-25.2) | 0.42 | 6.8 per 100p-y (95% CI 2.2-16.6) |

IQR = interquartile range; ** p-y = person years

### 4.7.2 Tuberculosis incidence & mortality of participants in IPT trial

Fifteen tuberculosis cases occurred in the randomized trial arms. In the randomised arms, nine (18.8%) of the 48 participants allocated to the INH arm developed tuberculosis compared with six (12%) of the 50 participants allocated to the placebo arm over a period of 24 months. Seven (46.7%) tuberculosis cases were diagnosed as definite, two (13.3%) were probable and six (40%) were possible (as previously defined).

**Figure 2: Kaplan-Meier analysis of the development of tuberculosis in RCT arms**




| Number starting interval/ Number of failures during interval | Baseline | 6 months | 12 months | 18 months | 24 months |
|---|---|---|---|---|---|
| INH | 48 | 36/5 | 24/1 | 15/2 | 7/1 |
| Placebo | 50 | 38/1 | 22/4 | 15/1 | 11/0 |

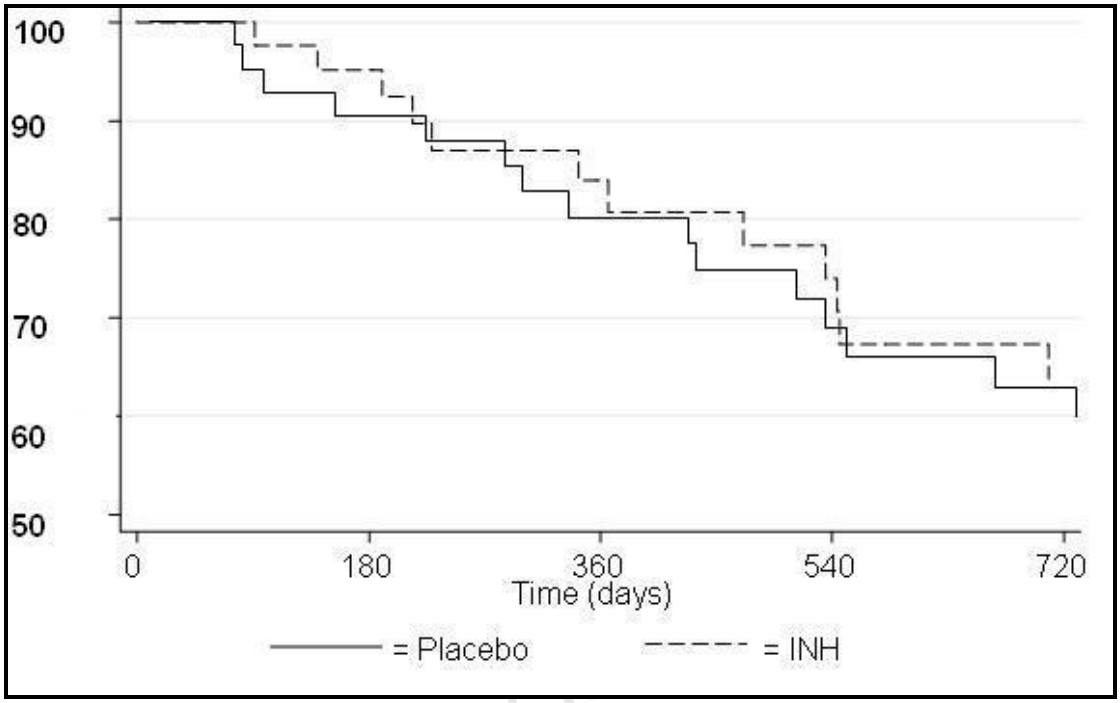
The overall tuberculosis incidence by any definition among the two groups of the closed label arms was 14.7 per 100 person-years (95% CI: 8.2 - 24.2). In the INH group it was 18.0 per 100 person-years (95% CI: 8.2 - 34.1) compared to 11.6 per 100 person-years in the placebo group (rate ratio 1.55; 95% CI: 0.49 - 5.30, p = 0.42). The overall tuberculosis incidence rate by any definition among the open label INH group was 6.86 per 100 person-years (95% CI: 2.18 - 16.56). There was no difference if the results were restricted to definite/probable tuberculosis cases.

Mortality from any cause was compared using the Kaplan-Meier survival graphs as shown in Figure 3. The Log rank test had a p-value = 0.598 (survival proportion) for the comparison of randomized groups. There was thus no significant difference observed between the INH and placebo groups in overall mortality.

The Cox proportional hazards model of risk of tuberculosis infection by randomised trial arms, in univariate (unadjusted) form, is presented in Table 18. The results are presented as Hazard Ratios (HR) and corresponding 95% Confidence Intervals (CI). The only statistically significant predictor was a history of tuberculosis five years or more prior to enrolment to the trial.

**Figure 3: Kaplan-Meier analysis of all cause mortality in RCT arms**

**Survival and mortality**




| Number starting interval / Number of failures during interval | Baseline | 6 months | 12 months | 18 months | 24 months |
|---|---|---|---|---|---|
| INH | 48 | 23/4 | 23/3 | 19/3 | 14/2 |
| Placebo | 50 | 31/4 | 24/4 | 21/3 | 17/4 |

Table 18 presents the risk of tuberculosis infection in the randomised trial arms, in a hazards univariate model of risk of tuberculosis by randomized arms. Age was not included since it did not fit into the model and nor did it yield a significant outcome. The p value for trend of three or more categorical variables was done (i.e. BMI & income) and nor did this yield a significant outcome, because of the small size.

**Table 18: Cox Proportional Hazards Univariate Model of risk of tuberculosis by RCT arms**

| Variable | HR | 95% CI | p value |
|---|---|---|---|
| Trial arm (INH versus Placebo) | 1.59 | 0.57-4.49 | 0.38 |
| Participant sex [Female=1; Male=0] | 1.01 | 0.37-2.79 | 0.98 |
| Baseline CD4 count [per 50 cell increase] | 1.05 | 0.87-1.27 | 0.61 |
| Baseline WHO stage [stage 4=1; Stage 3=0] | 1.56 | 0.55-4.45 | 0.40 |
| Employed [Unemployed/Housewife=1; Work/Student=2] | 0.58 | 0.19-1.71 | 0.58 |
| BMI: Overweight baseline (any category*) | 1 | Reference | - |
| Obese/Obese/Excessively Obese | 0.78 | 0.26- 2.32 | 0.43 |
| Normal | 1.15 | 0.23-5.62 | 0.93 |
| Malnourished | | | |
| Income: Wholly dependent | 1 | Reference | - |
| < R1000.00 per household | 0.71 | 0.19-2.52 | 0.59 |
| ≥ R 1000.00 per household | 0.53 | 0.14-1.98 | 0.93 |
| Karnofsky Score: Score 50-70 | 1 | Reference | - |
| Score 80 | 1.19 | 0.31-4.56 | 0.80 |
| Score 90 | 0.94 | 0.14-3.14 | 0.92 |
| History of TB (≥ 5 years prior to enrolment to trial) | 4.02 | 1.41-11.45 | 0.01 |
| Contact TB Household case | 0.29 | 0.38-2.19 | 0.23 |
| Social Class | 1.26 | 0.45-3.54 | 0.66 |
| Hospital Events (hospitalisation of participant) | 1.94 | 0.68-5.51 | 0.21 |

***** Overweight baseline (any category*): Slightly Obese/Obese/Excessive

Table 19 presents the risk of tuberculosis infection in the randomised trial arms, in a multivariate Cox HR model adjusted for all covariates with corresponding 95% confidence intervals.

**Table 19: Cox Proportional Hazards: Multivariate Model of risk of tuberculosis by trial arms**

| Variable | HR | 95% CI | p vale |
|---|---|---|---|
| Trial arm [INH = 1, Placebo = 0] | 2.02 | 0.65-5.23 | 0.22 |
| Participant sex [Female = 1; Male = 0] | 1.02 | 0.55-2.93 | 0.98 |
| Baseline CD4 count [**per 50 cell increase**] | 1.06 | 0.83-1.34 | 0.66 |
| Baseline WHO stage [Stage 4 = 1; Stage 3 = 0] | 1.56 | 0.55-4.45 | 0.40 |
| History of TB (5 years prior to enrolment to trial) | 3.48 | 1.11-10.92 | 0.03 |



### *4.7.2.1 INH/placebo adherence*

The administration of intermittent supervised INH/placebo and Pyridoxine adherence was measured by pill count on the monthly clinic visit and the monthly patient nominated supervision tick sheet. A strong correlation was observed between Pyridoxine adherence and INH/ Placebo adherence ($r = 0.97$, $p < 0.0001$).

There was no statistically significant change ($p=0.11$) in the median adherence of INH over time assessed quarterly in the randomised trial arms. There was a good correlation between pill counts and the monthly tick sheet by the patient-nominated supervisor (Spearman's ($r^2=0.704$). The median INH adherence in the randomised trial arms was 85% (not significantly different in the INH and placebo arms) and 92% in the INH open label arm. However, INH/placebo adherence was significantly higher ($p = 0.04$) among participants with a work-based patient-nominated

supervisor (87.3% by the monthly pill count) than compared with the home- or community-based patient-nominated supervisors (76.7% and 71.1% respectively).

In a multivariate logistic regression model of predictors for adherence (Table 20) the following factors were found to be associated with high adherence (≥ 80% adherence): lower age, INH open label, work-based supervisor, higher social class and participants who had completed secondary schooling.

**Table 20: Multivariate predictors of ≥ 80% adherence to INH**

| **Variable** | **Adjusted Odds Ratio** |
|---|---|
| Age (continuous) | 0.97 (95% CI: 0.92 – 0.99) |
| Race (Black vs. other groups) | 0.55 (95% CI: 0.21 -1.46) |
| **Randomisation arm** | |
| Placebo | 1.0 (Reference) |
| INH | 1.38 (95% CI: 0.56 – 3.40) |
| Open-label | 5.79 (95% CI: 1.47 – 22.75) |
| **Supervisor category** | |
| Home-based | 1.0 (Reference) |
| Community-based | 0.76 (95% CI: 0.26 – 2.25) |
| Work-based | 5.76 (95% CI: 1.47 – 22.75) |
| Social Class (I – III vs. IV – V) | 2.61 (95% CI: 1.05 – 6.481 |
| Did not complete secondary school | 0.37 (95% CI: 0.148 – 0.92) |
| Employed | 0.43 (95% CI: 0.16 -1.12) |

#### *4.7.2.2 Adverse effects of INH*

No major adverse effects of INH were observed among the 68 participants that received INH. However, three (2.5%) with mild peripheral neuropathy were reported in the randomised INH arm and none in the placebo arm (p = 0.114; Fisher exact test). No cases of hepatitis occurred.

#### *4.7.2.3 Adverse effects due to cotrimoxazole*

Four (3.4%) participants were identified as having had adverse effects to cotrimoxazole prior to enrolment and three (2.6%) participants developed adverse effects to cotrimoxazole while on the IPT trial and cotrimoxazole was stopped for these participants. These adverse effects were skin rashes.

#### *4.7.2.4 Cotrimoxazole (CTX) Adherence*

Cotrimoxazole adherence was measured during the monthly clinic visit by means of a pill count in both the open and closed label arms. The Shapiro-Wilk W test was used to test for the normality of adherence in the INH and the cotrimoxazole groups. Neither INH nor cotrimoxazole adherence was normally distributed and hence the Wilcoxon Matched Pairs Test was used to test any difference between the two groups.



The median cotrimoxazole adherence [73.5%; (IQR) 58.3-83.9] of participants in the randomised trial arms was significantly lower (p = 0.026) than the median cotrimoxazole adherence [84.6%; (IQR) 70.2 - 88.9] of the participants in the INH open-label arm, based on the Mann-Whitney test. However, there was no statistical difference (p = 0.831) between the median of SAT of cotrimoxazole adherence in the (INH closed-label arms) INH arm [73.7%; (IQR) 57.3-84.4] as compared to the placebo arm [73.5%; (IQR) 58.6-80.9]. The median cotrimoxazole adherence by SAT of

all three arms (including the open-labelled INH arms) was [73.3% (IQR) 61.4, 84.5],

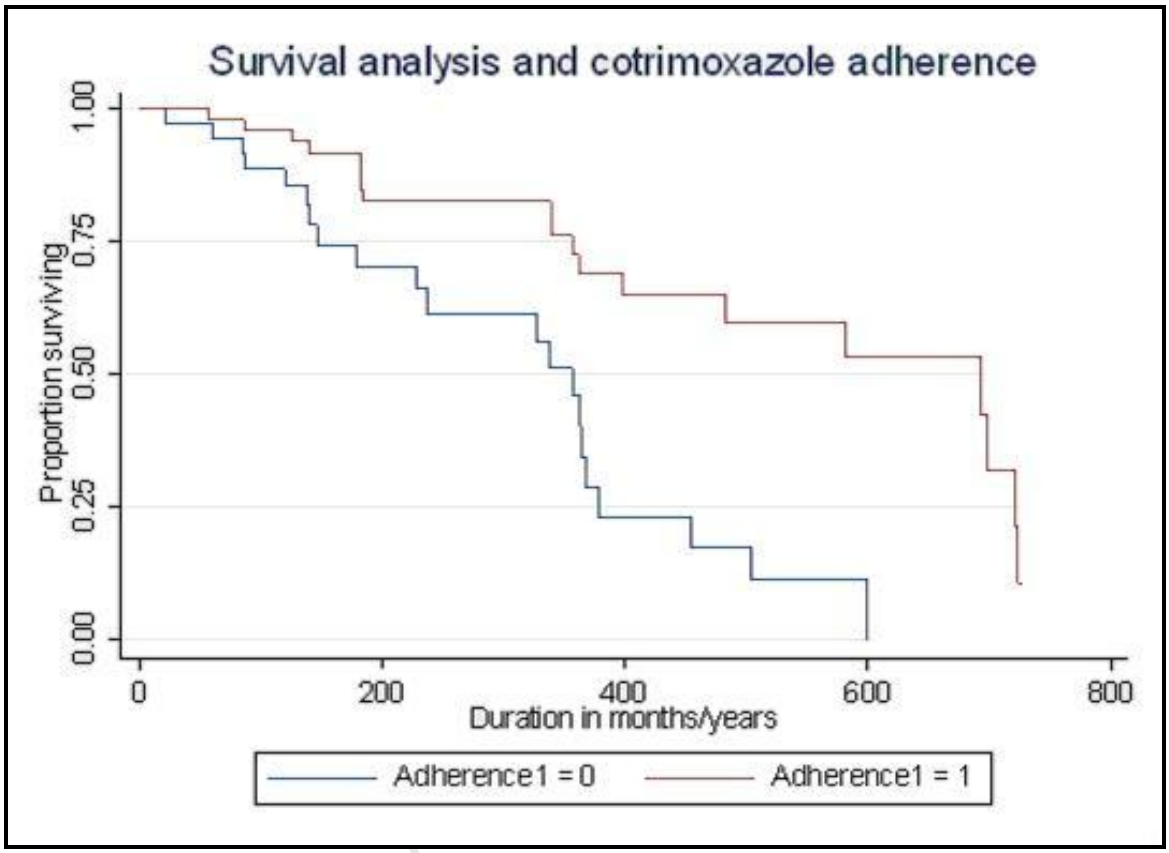
However when the median intermittent supervised INH adherence of [83.9% (IQR) 66.7, 92.5] in the closed-labelled arms was compared to the median daily SAT of cotrimoxazole adherence in all three arms [73.3% (IQR) 61.4, 84.5) among the same participants, it was higher Thus intermittent supervised INH adherence in the closed-labelled arms had a significant statistically higher ($p < 00.1$) adherence than the daily SAT of cotrimoxazole adherence in all three arms of the same participants.

Figure 4, shows that survival of participants with a threshold of ≥70% cotrimoxazole adherence (good adherence) had a significantly ($p = 0.0002$) better survival than those participants with a threshold of <70% cotrimoxazole adherence (poor adherence).

The participants with a poor cotrimoxazole adherence had a survival rate of 50% at one year as compared to a 75% survival rate among participants with good cotrimoxazole adherence.

However, the result shows that mortality in the <70% cotrimoxazole adherence group was lower but not significant as compared to the ≥70% cotrimoxazole adherence group (HR 1.28; 95% CI: 0.59 – 2.70). The large confidence interval indicates that the sample size is small when using death as an outcome.

**Figure 4: Kaplan-Meier analysis of cumulative proportion of survival comparison between participants of < 70% Cotrimoxazole adherence group (0) and ≥ 70% Cotrimoxazole adherence group (1)**




<70% Cotrimoxazole Adherence Group:

≥70% Cotrimoxazole Adherence Group:

p = 0.0002

# CHAPTER 5: DISCUSSION

## 5.1 Main findings

### 5.1.1 Tuberculosis screening instrument

The tuberculosis screening instrument of two or more symptoms developed in this study was able to detect 11 active tuberculosis cases in adults (8.5%) with clinically advanced HIV disease who had previously been assessed for active tuberculosis by the referring clinicians.

A simple screening instrument of two or more of symptoms (persistent cough, night sweats or fever) plus documented weight loss is thus capable of detecting tuberculosis in this population. This screening instrument had a sensitivity of 100% and specificity of 88.1%, (against the 'gold standard' of tuberculosis culture) and had positive and negative predictive values of 44% and 100% respectively (likelihood ratio positive 8.43).



### 5.1.2 IPT trial

There was no detection of any benefit of INH prophylaxis in TST negative participants with clinically advanced HIV disease for the primary end point of tuberculosis. There was no significant (p = 0.32) difference in the deaths 9all causes) between the INH closed-labelled arm and the placebo arm. Nor was there any significant difference in hospitalization of participants during the 24 months follow-up period with the 45.9 per 100 p-y in the INH closed-labelled arm, as compared to 46.3 per 100 p-y (p = 0.99). The median CD4 µL count the INH closed-labelled arm at 12 months follow-up was -28; IQR: -201 -- 692 as compared to -32; IQR: -234 – 239 (p = 0.31).

### 5.1.3 Adherence

There was a good correlation between pill counts and the monthly tick sheets completed by the patient nominated supervisors. This confirmed the inter-method reliability of the two methods of measuring supervised intermittent adherence to INH/placebo (Sumartojo E, 1993). Adherence was 85% in the randomized arms and 91.7% in the INH open arm. There was no statistically significant change in the median adherence of INH over time assessed quarterly in the randomised trial arms. The good INH adherence was attributed to the patient-nominated supervisors.

Adherence was significantly higher among the participants with work-based treatment supervisors than among those with home or community-based supervisors.

The adherence to the daily SAT of Cotrimoxazole by participants in the randomised trial arms (INH/placebo closed arms) was significantly lower than that by the participants in the INH open label arm. The reason for this difference could be that participants in the INH open label arm were in the less advanced disease stage. Furthermore, the participants in the INH open label arm were TST positive had observed the PPD induration on their arm prior to enrolment which could have been a strong motivating factor in them being more adherent.

Although the median (of all three arms) adherence to cotrimoxazole was good (73.3%; IQR: 61.4 - 84.5), the median INH adherence in all three INH/Placebo arms (among the intermittently supervised participants) was significantly higher. This difference may be important as pparticipants with a cotrimoxazole adherence >= 70 had a statistically significant higher survival rate than those participants with a cotrimoxazole adherence <70%.

This difference between median intermittent supervised INH adherences in the closed-labelled arms as compared to the median daily SAT of cotrimoxazole adherences in all three arms among the same participants could be attributed to many factors.

Firstly the comparison was made between intermittent supervision of INH/placebo as compared to the daily self administration of cotrimoxazole by the participant. Secondly, the adherence was calculated based on different dosages required dosage for INH and cortimoxazole. And thirdly the different type of medication (size, shape, taste and taste) of INH/placebo and cotrimoxazole could also have been another contributing factor to the difference in adherences between the supervised and self administered medication among the same participants.

However, when the median intermittent supervised INH adherence of [83.9% (IQR) 66.7, 92.5] in the closed-labelled arms was compared to the median daily SAT of cotrimoxazole adherence in all three arms [73.3% (IQR) 61.4, 84.5) among the same participants, it was higher Thus intermittent supervised INH adherence in the closed-labelled arms had a significant statistically higher ($p < 00.1$) adherence than the daily SAT of cotrimoxazole adherence in all three arms of the same participants.

One should bear in mind that missing a 900mg dose of INH administered twice a week would be equivalent to missing ~ 3 doses of daily INH (300mg). Therefore, although adherence was better with supervised IPT compared to self administrated CTX (85% vs 73.3%), the (estimated) effective adherence to IPT and CTX is similar (72,6% vs 73.3%). This point should be discussed

## 5.2 Limitations

### 5.2.1 Tuberculosis screening study

One study (Finch D & Beaty C, 1997) has shown that a single sputum culture specimen has been shown to be sufficient to establish the diagnosis of pulmonary tuberculosis in HIV-infected patients. However, participants with extra-pulmonary tuberculosis, as in one of the cases in this study, would not be detected using sputum culture only. It is thus possible that we may have under diagnosed tuberculosis during the screening process. Thus the limitation of using culture positive only as a 'gold standard' versus applying case definitions to TB cases which would allow one to exclude false positive cultures and include TB cases that are smear and culture negative, but have documented response to treatment.

A limitation on generalisability of this study is that the patient selection process was hospital based, consisting only of patients with advanced HIV disease. Also clinicians were referring patients who had already been previously screened routinely for tuberculosis and who referred patients to the trial whom did not suspect to have active tuberculosis.

It is possible that the investigator who reviewed the radiographs may have underreported chest abnormalities as the pathology of tuberculosis is different and may be difficult to interpret in adults with advanced HIV infection. A South African study at a VCT Centre found that only 44% of patients with confirmed PTB during screening prior to preventive therapy had suggestive findings on chest radiographs (Naidoo, P *et al,* 2002). Thus underreporting of tuberculosis based on chest abnormalities of chest radiographs alone my have occurred in this study.

Of the 11 active cases of tuberculosis only one case was identified as extra pulmonary tuberculosis based on the tuberculosis symptom screening instrument and the chest radiographs in addition to the radiologist were reviewed by an independent clinician as well. However, undetected extra pulmonary tuberculosis cannot be ruled out despite the fact that there were no active tuberculosis cases detected in participants within the first three months of entry to the trial.

### 5.2.2 IPT trial

The lack of efficacy of INH prophylaxis suggested by these results may be due to the limited statistical power of the trial. The major limitation of our study is that it was underpowered to detect a clinically significance (an intervention that makes a genuine, palpable, practical and noticeable difference to the everyday lives of the participants in the trial) in the reduction in tuberculosis incidence attributable to INH. In our calculation of sample size we assumed that nearly all participants would have LTBI (i.e. that the findings in TST positive subjects in other studies would apply to our participants), and we estimated an 80% reduction in tuberculosis incidence based on the only placebo-controlled trial that evaluated 12 months of INH (Hawken MP *et al,* 1997).

Therefore it is likely that we over-estimated the efficacy of INH in this sample size calculation. In a meta-analysis pooling the results of the Hawken study of 12 month INH prophylaxis with those of three other studies of 6 months of INH, the reduction in tuberculosis incidence was 62% in TST positive subjects (Woldehanna S & Volmink J, 2004). In addition, in our study there were high rates of death and loss to follow up among study participants, which is not unexpected as participants had advanced HIV disease and at the time no public sector access to antiretroviral therapy.

The incidence of tuberculosis in this study was also substantially lower than had been previously reported (Wood R, Maartens G & Lombard CJ, 2000). This could have been due to under-diagnosis of tuberculosis, but this is unlikely given the comprehensive diagnostic measures taken (symptom screening at each visit, and 6-monthly sputum culture and chest radiograph).

A more likely explanation for the lower than expected tuberculosis incidence could be because of the prior exclusion of potential participants with a history of tuberculosis within the previous five years. These individuals are likely to have had a greater risk of developing tuberculosis than individuals admitted into this study. This possibility is supported by our finding that previous tuberculosis was associated with an increased risk of recurrent tuberculosis (HR 3.48; 95% CI: 1.11-10.92). This has been shown in other local studies. For example, in a study of HIV-infected South African gold miners, previous tuberculosis approximately doubled the risk of another event of tuberculosis (Grant A *et al,* 2005). It is also possible that unrecorded or tuberculosis could have been a possible cause of death or loss to follow up in some of the participants in this trial.

Secondly the lower than expected incidence of tuberculosis during the follow-up could also have been contributed by the fact that all participants were screened for tuberculosis prior to their entry to the trial and in the first three months of follow-up of these participants, there were no tuberculosis cases diagnosed. Thirdly most participants prior to their death had left for their rural home to die. Hence the exact cause of death could not be established since no identity number of the participants was collected to confirm exact cause of death from the death certificates. And finally we had looked hard for tuberculoses did six monthly cultures of all participants on the trial and it is quite likely that we could have missed tuberculosis especially those participants that may have developed extra pulmonary tuberculosis.

It has been shown that the risk of active tuberculosis in individuals with a positive TST is increased by 12.9 cases per 1 000 in those who had been infected by this organism within less than one year as compared to 1.6 per 1 000 increase in those had been infected between 1 and 7 years previously. With HIV infection the active tuberculosis risk among recently infected individuals increased by 35 - 162 per 1 000 persons within this group (CDC MMWR 2000).

It is believed that had patients who had a history of tuberculosis less than five years prior to their entry to the trial and especially those of patients who had recently been treated for active tuberculosis may have decreased the event rate in this trial. Thus the increased the number of tuberculosis cases in both randomized arms (INH versus placebo), may have perhaps have enhanced the validity of the outcomes.

### 5.2.3 Adherence study

A limitation of adherence detection in this study was that adherence was not verified by routine or random urine analysis. However, the adherence to INH/placebo was verified by monthly pill count and compared with the monthly tick sheet of the patient-nominated supervisors. There was a good agreement between pill counts and the monthly tick sheets.

In a previous study (Whalen CC *et al,* 1997), of 97 participants who were randomly selected for a single urine spot check of INH at a home visit between clinic visits, 78 (80%) tested positive for INH. It was noted that those participants with a positive home spot urine test for INH had a higher proportion of positive INH tests at the regular clinic visit than those with negative urine test (82% versus 46%, $p < 0.001$).

As participants were required to nominate supervisors, some of whom had no knowledge of the participant HIV status, maintaining confidentiality became an issue. Patient-nominated treatment supervisors who were not aware of participant HIV status were informed that this was a trial to prevent tuberculosis. It cannot be ascertained whether the outcome with regard to adherence was different in those participants whose patient-nominated treatment supervisors who were aware of participant's HIV status compared to those treatment supervisors who were not aware.

The assessment of SAT cotrimoxazole adherence was also based on pill counts without the validation of routine laboratory assessment. However, we believe that this was not a major limitation, based on a study conducted by the National Tuberculosis Control Programme of Malawi. The cotrimoxazole pill count in that study (Zachariah R *et al,* 2001) was verified against gas chromatography/mass spectrometry (GC/MS) as a gold standard. This yielded a sensitivity of 91.5%, specificity 60%, PPV 97.4%).



## 5.3 Relationship to literature

### 5.3.1 Tuberculosis screening

The 11 (8.5%) active tuberculosis found among 129 adults (10 definite and 1 possible) with clinically advanced HIV disease is similar in proportion to that found in similar settings where tuberculosis is endemic. (Burgess A L *et al,* 2001; Aisu T *et al,* 1995 & Espinal MA *et al,* 1995).

In this study a simple screening instrument of symptoms and documented weight loss was capable of ruling out tuberculosis. A high sensitivity and negative predictive value, i.e. avoiding false negatives, is more important than specificity in a screening instrument for tuberculosis prior to initiating

tuberculosis preventive therapy. This is in order to prevent the development of drug resistance (WHO, 1999). The 88% specificity of the screening instrument means that 12% of patients (false positives) without active tuberculosis would be excluded from tuberculosis preventive therapy. Since the aim of screening is to exclude those patients with tuberculosis from IPT, the 12% exclusion of participants (without active tuberculosis) is a reasonable level of margin of error of the unintended exclusion of participants for IPT.

Kimerling and colleagues (Kimerling ME *et al,* 2002), found that using 'symptoms only' had a lower positive predictive value than in our study (Mohammed A *et al,* 2004). This may have been due to their different patient population who were all based in home care, or because weight loss was not measured. Despite this, 95% of their tuberculosis cases had reported symptoms (Kimerling ME *et al,* 2002). Active tuberculosis was also reported to be frequently found in screening for tuberculosis in HIV testing centres in developing countries (Aisu T *et al,* 1995; Espinal MA *et al,* 1995). Hence the integration of tuberculosis screening in high HIV and tuberculosis prevalence settings provide early diagnosis and treatment of tuberculosis as well as prevention and reduced risk of nosocomial infection (Burgess AL *et al,* 2001)

The WHO and the US Centers for Disease Control and Prevention recommend chest radiograph as a component of the screening process to exclude tuberculosis prior to preventive therapy in HIV infection (WHO, 1999; CDC MMWR, 2000). We found that chest radiograph did not improve the performance of the tuberculosis symptom screening instrument. However, in a recent study (Day JH *et al,* 2006) chest radiography did improve sensitivity of tuberculosis screening in a population of gold miners with WHO stage 1-4, with 46% of the participants in WHO stage 1. The reason for this outcome differing from our study could be attributed to the target group of participants HIV-

infected gold miners in South Africa being different from our study which included only WHO 3 and 4). The prospective study of chest radiograph in Botswana to screen for tuberculosis showed only 1 (0.2%) participant was diagnosed with tuberculosis and the study recommends that routine chest radiograph should not be routinely used for persons to be enrolled for IPT especially in settings which is able to screen for signs and symptoms of tuberculosis (Mosimaneotsile RN, *et al,* 2003)

### 5.3.2 IPT trial

The lower limit of the 95% confidence interval for the relative hazard of tuberculosis in TST negative participants receiving INH (0.57) rules out benefits associated with IPT, i.e. the 80% reduction which has been shown in previous studies of TST positive individuals (and which guided our sample size calculations). Thus this study has shown that lower limit of the 95% confidence interval for the relative hazard of tuberculosis in TST negative participants receiving INH are compatible with no effect and hence the outcome is neither clinically or statistically significant for those participants that are in the advanced stage of HIV-infection (WHO 3 & 4). Hence this study adds no evidence to refute the hypothesis that INH is ineffective in TST negative patients with advanced stage of HIV-infection**.**

The lack of IPT effect in this study, among participants (particularly those with lowest CD4 counts) could possibly be attributed to their high risk of death that may have resulted in them not having survived long enough to develop tuberculosis. And secondly, those participants that had died out of Cape Town or elsewhere, may have had undiagnosed tuberculosis, that may not have been detected just prior to their death. As indicated that the finding of this study is thus broadly consistent with previous meta-analyses of preventive therapy (Bucher HC *et al* 1999; Woldehanna S & Volmink J, 2004)

In HIV-infected patients TST are more likely to be negative as CD4+ lymphocyte count declines (Markowitz N *et al,* 1993) The risk of HIV-associated tuberculosis increases with advancing immune suppression as assessed by CD4+ lymphocyte count or disease stage (Holmes CB *et al,* 2006; Wood R, Maartens G & Lombard CJ, 2000). In areas endemic for tuberculosis such as the Western Cape, the majority of HIV-seronegative adults have LTBI as assessed by a positive TST (Rangaka MX *et al,* 2006). In this setting most HIV-infected patients with a negative TST would thus be anergic owing to advanced HIV disease, and thus at high risk of tuberculosis (Holmes CB *et al,* 2006; Wood R, Maartens G & Lombard CJ, 2000), rather than being uninfected with MTb. It is therefore surprising that treatment of LTBI has been shown to be ineffective in TST negative participants in trials conducted thus far (Bucher HC *et al* 1999; Woldehanna S & Volmink J, 2004).

This lack of effect in other studies could be explained by the fact that participants with advanced HIV disease were under-represented in the placebo-controlled clinical trials conducted in areas where tuberculosis is endemic (Pape JW *et al*, 1993; Hawken MP *et al,* 1997; Mwinga A *et al;* Fitzgerald DW, *et al,* 2001). TST negative participants in these trials could thus have been more likely to be “true negatives” (i.e. did not have LTBI).

Previous studies following standard 6-month treatment of PTB have estimated relapse rates to be 1% to 2% at 24 months (British Thoracic Association, 1982). Host factors such as sex, disease factors and treatment-related factors interact to cause relapse (Tam CM, *et al,* 2002). We would have excluded these high risk patients from our trial because of the five year tuberculosis history exclusion criterion.

A recent study showed that relapse occurred within one year after tuberculosis recovery in 74% of HIV-positive patients where the majority

were in the advanced stage of the disease. This was significantly higher than among HIV-negative patients (Domoua K, 2005). However, where HIV-infected patients received tuberculosis treatment for ≥ 9 months with the concomitant administration of HAART (resulting in undetectable viral load), the relapse-rate was 1.9/100 patient years (95% CI: 1.8 – 2.0) compared to those who had tuberculosis treatment of 6 – 7 months (with no HAART), the relapse rate was 42.8/100 patient years (95% CI: 39.1 – 46.5) (Lopez-Cortes LF *et al,* 2005). This tuberculosis relapse among patients receiving tuberculosis treatment for ≥ 9 months was similar to that observed in non immuno-compromised patients who received the standard 6-month anti-tuberculosis regimen (Chaisson RE *et al,* 1996). Hence, as the result of the entry criteria of selecting trial participants who had a history of tuberculosis of five years or more may have impacted on the outcome tuberculosis among participants in the trial.

Tuberculosis patients cured by short course treatment in trial conditions had at least a 7% recurrence of tuberculosis within 1 - 2 years (El-Sadr WM *et al,* 2001). A study in a high-incidence area where tuberculosis was successfully treated showed the risk of reinfection was approximately 2% per annum. The rate of reinfection resulting in tuberculosis was approximately seven times the crude incidence rate and approximately four times the age-adjusted incidence rate of tuberculosis. The likely reinfection disease rate/100 person years in this study was 2.4 (95% CI: 1.4 – 3.8) and 1.4 (95% CI: 0.5 – 3.3) for those that were cured and completed treatment respectively (Verver S *et al* 2005).

Yew (Yew WW, 2005) has proposed that the selection of individuals with predisposition to tuberculosis infection/disease or that tuberculosis itself increases the vulnerability or both these factors may possibly explain the increased vulnerability of HIV positive patients treated for tuberculosis as compared to HIV negative patients treated for tuberculosis. This view is supported by the investigation undertaken by Glynn JR and colleagues

where it was demonstrated that a higher proportion of recurrent tuberculosis was caused by reinfection among HIV-positive individuals for tuberculosis as compared to the HIV-negative individuals (Glynn R, *et al* 2004).

### 5.3.3 Adherence

#### *5.3.3.1 INH/placebo*

The strength of our study was the high level of INH adherence which was higher than in most other trials reporting adherence (Hawken MP *et al,* 1997; Mwinga A *et al,* 1988; Whalen CC *et al,* 1997). A recent cohort study of adherence to preventive therapy for HIV-infected patients in rural South Africa showed poor adherence, with only 47% patients completing treatment (Rowe KA *et al,* 2005).

Our study did not have a clinic DOTS comparison group. However, a Cochrane Review (Volmink J & Garner P, 2006) of DOTS for treating tuberculosis concluded that there was no statistical difference in treatment outcome of cure or treatment completion between DOT and self treatment arms. There was also no difference in cure or treatment completion between family member and clinic supervision.

The medications of INH/placebo in the previous seven trials of TST negative adults with advanced HIV disease were all self-administered in contrast to our participant nominated treatment supervisors.. The adherence in these trials varied greatly and did not achieve the high adherence we achieved in this trial. In three of these trials (Pape JW *et al,* 1993; Gordin FM *et al,* 2000; Fitzgerald DW *et al,* 2001), no mention of monitoring and adherence to trial medication of participants was made.

Hawken and colleagues (Hawken MP *et al,* 1997) measured INH versus placebo adherence by tablet count at scheduled visits, the total number of weeks missed of trial medication in six months as well as random urine tests by a technician blinded by the trial code. Although there was no significant difference in effect of INH on tuberculosis incidence across the three levels of adherence measurement, the overall adherence in this trial was poor. The estimated number of treatment weeks missed by participants for one week, 1 - 4 weeks and > 5 weeks was 281 (41.7%), 183 (27.1%) and 210 (31.2%) respectively. Of the 315 participants receiving INH, 70% had at least 50% positive urine tests.

#### *5.3.3.2 Cotrimoxazole*

We believe that this is the first study that compares the good and poor level of cotrimoxazole adherence in relation to the mortality among adults with advanced HIV disease, where the threshold of ≥70% cotrimoxazole adherence has shown a statistically significant higher survival rate than participants with the threshold <70% CTX adherence.

The cotrimoxazole adherence in our study where 62.2% of participants had a (median ≥70%) cotrimoxazole adherence that was relatively better than a previous study conducted by CDC in Uganda (Lule JR *at al,* 2002) where adherence was excellent for 42% of participants, good for 41% and poor for 17% by pill count. In a cohort study Rwanda to (Nagaba W *et al*, 2004) to assess the feasibility of the use of cotrimoxazole prophylaxis and drug adherence showed that a total of 60 patients (36%) admitted to have taken their doses as expected. Whereas the study (Hausler HP *et al* 2002) of IPT and cotrimoxazole in South African pilot districts, adherence to six months of cotrimoxazole prophylaxis varied from 5% in Ugu South to 32% in Bushbuck Ridge to 64% in Central District.

The possible reason why cotrimoxazole adherence was good in this study (with majority of participants in the threshold of ≥70% cotrimoxazole adherence, could be attributed to counseling of the participant on enrolment on the need to adhere strictly to their prescribed medication. This message was reinforced with an appropriate message on the specially designed clinic card for the participant's enrolled on the RCT. These clinic cards in addition to indicating the scheduled dates of the monthly clinic visits of the participants had also an enforcing message on the need for participants to be adherent and reiterated that tuberculosis was preventable, treatable and curable if medication was taken regularly as prescribed (Appendix 3).

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A study by Balestra and colleagues (Balestra P *et al,* 1996) showed in a multiple logistic regression analysis a significant association of non-adherence with a CD4+ count less than 100/$mm^3$ (OR:4.7,95% CI:1.2-10.1) and cotrimoxazole prophylaxis (OR:2.5,95% CI:1.1-5.8). This study identified during the interview reasons for non adherence could be attributed to belief of ineffectiveness of the drug; denial of the HIV status; self-perception of adverse effects. We have during the enrolment process and at the monthly clinic visit of the participant have adequately addressed these factors on an ongoing basis.



The reason for the overall cotrimoxazole adherence (all three arms) to being significantly lower than the adherence among the same participants in the INH/Placebo groups (including open INH arm) is presumably because the INH/placebo was supervised whereas the cotrimoxazole was SAT on a daily basis. However, the reasons for cotrimoxazole adherence being significantly higher in the INH open-label arm than the cotrimoxazole adherence in the randomised arms could be attributed to the participants having observed their PPD induration which confirmed

their TST positive. Thus this group of participants were informed that they were at risk of developing tuberculosis and were required to strictly adhere their prescribed medication (including SAT cotrimoxazole, since this medication was known to reduce the risk of the development of tuberculosis. Thus the observation of PPD induration by the participant may have positively enhanced their perceptions of the severity of their illness and risk of developing opportunistic infections, as well as a positive attitude toward the healthcare system and their perceived relationship with the healthcare provider (Hall RA *et al,* 2001).

The assessment of the SAT cotrimoxazole adherence, based on pill counts without the validation of routine laboratory assessment was a limitation in this study. However, we believe that this may not have been a major limitation since a study conducted by the National Tuberculosis Control Programme of Malawi. (Zachariah R *et al,* 2001) showed that pill count of cotrimoxazole was verified by gas chromatography/mass spectrometry (GC/MS) as a gold standard which yielded sensitivity of 91.5%, specificity 60%, PPV 97.4%).

The number of adverse effects to cotrimoxazole among the participants in our trial were reported to be seven (5.9%) of whom four participants had adverse effects prior to enrolment to the trial and three (2.6%) participants developed skin rash. while on the IPT trial. This result is consistent with study (Zachariah R *et al*, 2003) in Malawi, where tuberculosis patients diagnosed with HIV were administered cotrimoxazole and 2% were reported to have skin rash.

## 5.4 Conclusions

This study has demonstrated that a simple screening instrument can effectively detect tuberculosis in patients with advanced HIV disease in a

hospital based setting. Once tuberculosis has been excluded, TST can be done to assess eligibility for preventive therapy.

We have shown that patient nominated supervisors for preventive therapy, and particularly if based in the workplace, are effective and practical for resource-limited settings. Randomised studies of patients with tuberculosis thus indicate that directly observed therapy supervised by guardians or family members is at least as effective as supervision in the clinic or community. Cotrimoxazole by SAT also had good adherence especially among the TST positive participants with greater benefit in survival among participants with ≥70% adherence. There were minimal adverse events (of skin rash) consistent with previous studies.

However, we found no benefit associated with INH preventive therapy in participants with clinically advanced HIV and negative TST in an area with a very high tuberculosis incidence. Although our findings are consistent with meta-analyses, they should be interpreted with caution owing to our small sample size. Access to antiretroviral therapy is rapidly increasing in resource-limited settings and an important research question is the role of INH or other preventive therapy in patients receiving combination antiretroviral therapy.

The daily SAT cotrimoxazole showed a good adherence especially among the TST positive participants. This study also shows that there was a greater benefit in terms of survival among participants with a threshold of ≥70% CTX adherence. There were minimal adverse events which was consistent with previous studies (Ioannidis JP *et al*, 1996; Schneider MM *et al*, 1992),

## 5.5 Recommendations

The WHO and the US Centres for Disease Control and Prevention recommend chest radiograph as part of the screening process to exclude tuberculosis prior to preventive therapy in HIV infection (WHO, 1999; CDC, MMWR 2000). Chest radiographs alone in this study had a sensitivity of 27%. Hence it is recommended that chest radiography as part of TB screening, based on the results of this study can only apply to HIV-infected individuals with advanced HIV disease.

Active tuberculosis case finding should be an integral component of HIV management at primary care and VCT Centers (Naidoo P *et al,* 2002). We have demonstrated that a simple screening instrument can effectively exclude tuberculosis in patients with advanced HIV disease. Once tuberculosis has been excluded, TST can be done to assess eligibility for preventive therapy. As in our study, nurses could apply the screening instrument.

Based on the good adherence observed in this study, it is recommended that since patient nominated supervisors are effective and practical for resource-limited settings they should become an integral part of IPT, at least in adult patients.

Although no benefit was associated with IPT in participants with clinically advanced HIV and negative TSTs, (consistent with meta-analyses), access to antiretroviral therapy (ART) is increasing in resource-limited settings and hence there is a need for further investigation of the role of INH or other preventive therapy in patients receiving combination antiretroviral therapy.

## 5.6 Research

A recent survey of international public health agencies highlighted the need for four additional interventions needed to control HIV related tuberculosis (Maher D *et al,* 2005). Two of these four interventions were tuberculosis preventive therapy and intensified tuberculosis case finding.

The Maher (Maher D *et al,* 2005) review has further identified the need to focus on the cost effectiveness of screening LTBI. Such research needs to determine the number of persons with LTBI for IPT needed to prevent one case of tuberculosis as well as focus on methods of effective screening for extra-pulmonary tuberculosis prior to enrolling patients on IPT.

Although, it is more important to exclude active undiagnosed TB prior to starting IPT monotherapy, which may generate resistance, there is no data to date to support whether poor adherence to IPT could lead to INH resistant TB. In theory, poor adherence to IPT could lead to INH resistant TB. Hence, another research focus area could be to determine the association of poor adherence and IPT resistance, since good adherence is important to maximize the effectiveness of IPT.

Based on the results of this IPT trial we recommend that the tuberculosis screening study be replicated in a clinic setting in a form of operational research, with trained nurses using this screening instrument. In addition, the validity and cost effectiveness of using a simple tuberculosis screening for active tuberculosis case finding at Primary Care and VCT Centre level and not only for referred patients with advanced HIV, need to be tested.

Although, the study demonstrated no benefit associated with IPT among participants with clinically advanced HIV and negative TSTs, this result should be viewed with reserved degree of uncertainty because of the under powering and the exclusion of patients to the study with ≤5 years history of tuberculosis on entry to the trial. Hence any future studies in this regard should take cognisance of these two factors.

# CHAPTER 6: EPILOGUE

## 6.1 The way forward?

The spectre of a more deadly form of MDR-TB termed XDR-TB that was reported in Kwazulu-Natal (the province in South Africa with the highest HIV prevalence), in January 2006 (WHO 2006), is an indictment of the failure of the NTBCP. By February 2007, 269 XDR-TB cases had been reported in South Africa, which spread to all nine provinces, and an estimated mortality rate of 85% (Kapp C, 2007).

The emergence of XDR-TB does not augur well for the Global Tuberculosis Control Programme, especially for developing countries such as South Africa with one of the highest HIV prevalence in the world. South Africa has in excess of five million HIV positive persons that are potentially at risk of being infected with XDR-TB.

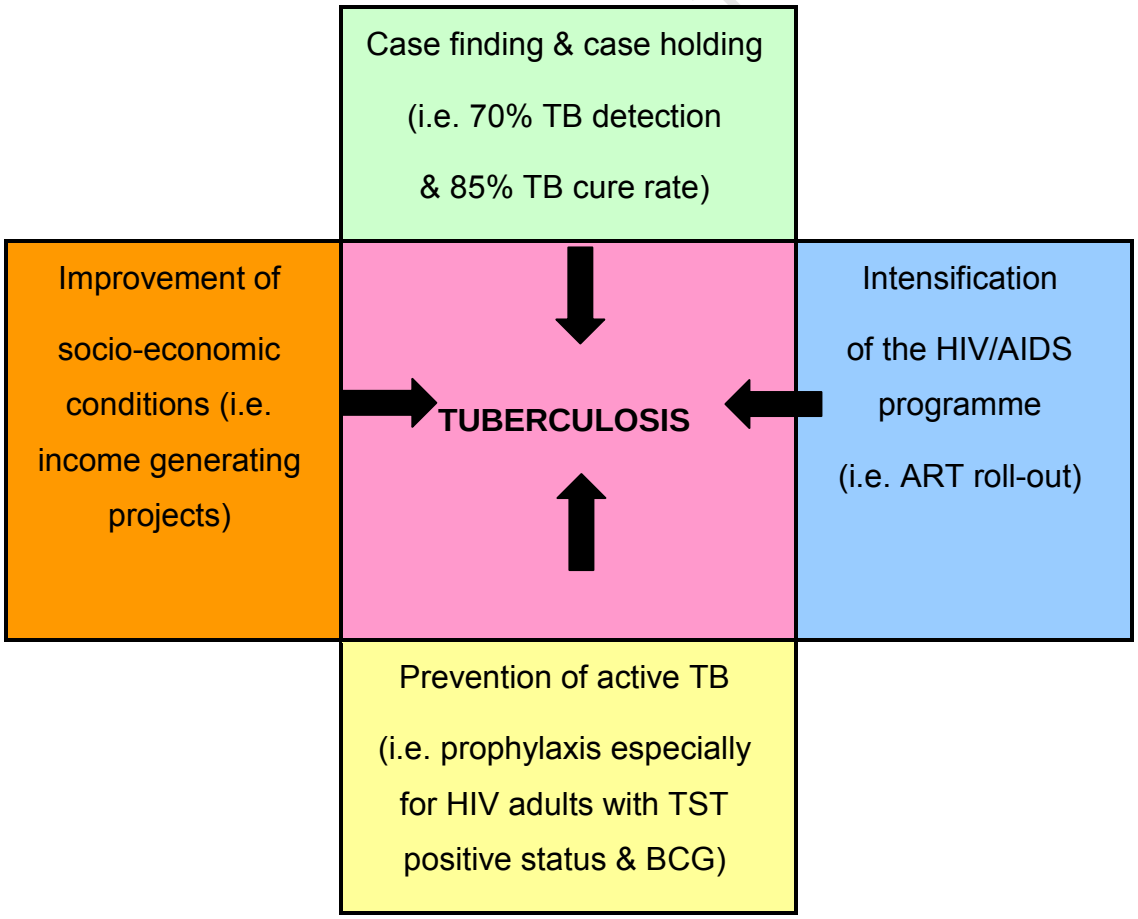
Although South African health legislation is empowered to detain those with infectious disease until it is no longer a threat (in line with WHO guidelines), this is not a viable option. This would further exacerbate the stigma associated with tuberculosis and HIV.

The emergence of XDR-TB with the need to use of detention as an isolation measure thus threaten to undermine any attempts in the prevention, control, management and care of patients with tuberculosis, MDR-TB or XDR-TB.

To effectively begin to deal with MDR-TB and XDR-TB requires a return to the basics of the prevention, control and management of the tuberculosis Control Programme. Figure 5 outlines a four pronged strategy in combating tuberculosis, focusing on tuberculosis case finding and case holding (i.e. incorporating 70% tuberculosis detection rate and 85% tuberculosis cure rate with the DOTS strategy); the prevention of tuberculosis by prophylaxis (in most vulnerable groups) and BCG (in children to prevent tuberculosis meningitis); improvement of socio-economic conditions (skills building and income generating projects) and the intensification of the HIV/AIDS strategy (especially the treatment programme).



**Figure 5: The Four Pronged Tuberculosis Strategy**




**Source: Mohammed, A. Towards the conquest of TB in the 21st century. Conference paper presented at the International Conference (TB Strategies for Africa): 18-20 October 2000, Cape Technikon, Cape Town**.

I am of the firm belief that instituting these four strategies religiously and calling on all intersectoral stakeholders we could substantially control tuberculosis, HIV/AIDS, MDR-TB and XDR-TB.

It is my recurring nightmare that a day will soon dawn where South Africa, could as a result of its failure in the prevention, control and management of TB, HIV/AIDS, MDR-TB and XDR-TB, declare martial law because the wards of hospitals being filled to capacity with one or more of these diseases especially XDR-TB. South Africa would be unable to cope with the over-burdening morbidity and mortality rates and related costs exacerbated by succumbing to these four concurrent epidemics indefinitely. This would have dire consequences for this very young democratic country with such abundance of potential and resources. How many eyes will have to close into eternity before we open our eyes to this global public health emergency?



We are fortunate in knowing enough, early enough, to prevent such an impending catastrophe. But the time to act is now. In the words of Mario Raviglione (Director of Stop TB at WHO): *"The local, national and international response to the spread of XDR-TB was too little too late. This is an absolute emergency. It is the most urgent thing I have ever seen in my 15 years of working in tuberculosis: a highly resistant strain that is now killing HIV-positive people and spreading very rapidly… Nobody is moving fast enough* (Kapp C, 2007).

We have already seen the indicators for this impending catastrophe. On Friday 23 April, 1993 WHO declared tuberculosis a global public health emergency. Three years later, in 1996, Minister Ebrahim Rasool, the former MEC of Health of the Western Cape, (South Africa) declared tuberculosis a provincial emergency. In 2006 an outbreak of XDR-TB was reported in Kwazulu Natal, South Africa where 53 XDR-TB cases were

confirmed of which 44 patients were HIV-positive. Fifty two of the 53 patients died, on average, within 25 days. Now in 2007 XDR-TB has been reported in all nine provinces in South Africa.

What is next? Total drug resistant tuberculosis (TDR)? The implications of such an outbreak as is occurring with XDR-TB are unthinkable. But to avert this imminent 'holocaust' we need to act now while in this period of the window of opportunity.

*"Never before has Man had such a capacity to control his own environment; to end thirst and hunger; to conquer poverty and to end disease; to banish illiteracy; and massive human misery. We have the power to make this the best generation of mankind in the history of this world or the make it the last"*

**John F Kennedy (former US President: 1917-1963)**

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# APPENDICES

## Appendix 1

### *Participant informed consent form for INH/Placebo trial*

HIV slowly destroys an important White Blood Cell (CD4 cell). This weakens the body and allows the other germs to cause sickness. Many of these sicknesses can be prevented by taking tablets. Tuberculosis (TB) is most common sickness in patients infected with HIV in South Africa. This study will observe if TB or any other common sickness can be prevented among HIV-infected patients in Cape Town with the use of certain tablets under supervision of TB Supervisor whom you will be required to nominate.

TB can be prevented by using the tablet named isoniazid (INH). Studies have shown that INH prevents the development of TB in HIV patients who have been tested positive for skin test. Therefore, all HIV patients who are tested positive for a skin tests (enrolled in this trial) will receive INH every month for 12 months with the supervision of their nominated supervisor.

We believe that because TB is a very serious problem in Cape Town, that INH may also prevent the development of TB in HIV patients who have been tested negative for a skin tests. Because we are not sure if INH really works in HIV patients with negative skin test, some patients will get INH and others will get a placebo (looks like INH, but does not have effect like INH). Each patient participating in this trial will have an equal chance of receiving INH or placebo. All those involved in this trial (i.e. doctors, nurses, researchers, patients and supervisors), will not know who was allocated INH or placebo, until the completion of the trial.

At the beginning of the trial, you will get a TB skin test (a small injection on the under skin of your left arm) and on the right arm you will get a

multipuncture skin tests. You will also be tested to determine if you have TB. If you are confirmed to have TB, you will not be eligible for the trial but instead will be referred to the clinic nearest to your home for TB treatment.

On your enrolment to the trial you will be supplied with INH/placebo, vitamin (pyridoxine) and an antibiotic (cotrimoxazole) at each monthly clinic visit. The INH and vitamin tablets will taken by you twice weekly under the supervision of your supervisor for 12 months, whilst you will be required to take the antibiotic (cotrimoxazole) daily (without supervision) to prevent other common sickness. Studies have shown that this antibiotic does work in patients infected with HIV, so everyone on this trial will receive cotrimoxazole. This antibiotic can sometimes cause skin rash and you will be observed for any such reaction. If this happens this happens this antibiotic will be discontinued and replaced with another antibiotic.

INH can sometimes cause skin rashes or damage to the liver (causing nausea, or yellow colour in the eyes or brown colour in the urine) or damage the nerves (which will cause tingling or numbness in the feet). You will be checked for these problems every month and would be required to let your doctor, nurse, research or supervisor if these problems occur. You should not drink alcohol while on the study as this makes the problem of damage to the liver or nerves happen more often. If serious side effects to INH occur, you will be taken of the trial.

Entry to this trial is voluntary. Your refusal to enter and participate into this trial or your decision to discontinue participation in the trial at any stage will not prejudice your standard treatment that will be rendered to you on your regular visit to the HIV clinic. If you decide that you do not want to carry on with the study, you may do so. However the medication prescribed for you will be discontinued, but you will continue to get standard treatment from the clinic you had previously attended. If you were prescribed INH based

on the positive result of your skin test, you will continue to receive INH in addition to the standard treatment from the clinic you had previously attended.

On your decision to participate in this study, details of your sickness (HIV status) will not be revealed to anyone not directly involved in this trial including the treatment supervisor.

If you have any questions during this study, please feel free to contact:

Ashraf Mohammed at (telephone 404-9111, page 1503) or Prof Gary Maartens (telephone 404-9111, page 1306).

I, Doctor …… (please print) confirm that the risks and benefits of the trial (study) have been explained to the patient …… (please print) with following folder number ……

Doctor's signature…… Date: ……..

Patient's signature: …… Date: ……..

Witness signature:…….. Date: ……..

## Appendix 2

## *Part 1 - Questionnaire patient interview: Demographic & clinical history*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Name of Clinic | | | | Study ID Number | | | | |
| 1. Surname | | | | First name | | | | |
| 2. Date of Clinic Visit | Day | | Date | | Month | | Year | |
| 3. Type of Clinic Visit: | | | | | | | | |
| 4. Clinic Visit Number | | | | | | | | |
| 5. Name of hospital referred from (Tick response)<br>➢ New Somerset Hospital<br>➢ Groote Schuur Hospital<br>➢ Tygerberg Hospital<br>➢ Other (Specify) | | | | | | | | |
| 6. Name of Referring Dr | | | | | | | | |
| 7. Patients Hospital Folder Number | | | | | | | | |
| 8. Date of Birth | | | | | | | | |
| 9. Gender (Tick response)<br>➢ Male<br>➢ Female | | | | | | | | |
| 10. Race (Tick response): (a) White<br>(b) Coloured<br>(c) African<br>(d) Asian | | | | | | | | |
| 11. Residential address | Telephone…… | | | | | | | |
| 12. What is your marital status? (Tick response)<br>➢ Married<br>➢ Divorced | | | | | | | | |

- Separated
- Widow
- 'Common Law Marriage'
- Single

13. What is your Occupational Status (Tick response)

- Employed White
- Unemployed
- Pensioner
- Housewife
- Disabled
- Student
- Other (Specify ……)

**If unemployed,** are you on: (Tick response)

(a) Disability grant
(b) Pension
(c) Boarded
(d) Unemployment fund
(e) On severance package
(f) None of the above
(g) Other income (Specify ……)

**If employed,** are you: (Tick response)

(a) Permanent
(b) Temporary
(c) Part-time

14. What is the highest level you have reached in education? (Tick response)

- Primary
- Secondary
- Tertiary
- No Schooling

15. Have you had BCG? (Tick response)

- Yes
- No
- Don't know

16. Do you have any scarring on the arm (Tick response)

- Yes
- No

17. Have you ever in the past been diagnosed with tuberculosis?

(Tick response)

- Yes
- No
- Don't know

**If YES:**

- Was it TB of the lungs?
- Where were you treated?
- When were you treated?

18. Have any of your household members residing with you been diagnosed with TB in the last year? (Tick response)

- Yes
- No
- Don't know

**If YES:**

What is the household member's relation to you?

- Name:
- Age:
- Where was s/he treated?
- When was s/he treated?

19. What was your current /last employment status? (Tick response)

- Professional
- White Collar/Middle Management
- Skilled/Artisan
- Semi-skilled
- Unskilled
- Not applicable

20. Name the company where you last worked?

21. Workplace address & telephone?

22. Are you on Medical Aid? (Tick response)

- Yes
- No

**If YES:** Name of Medical Aid

23. Are you the sole supporter of your family/household? (Tick response)

- Yes
- No

24. What is your monthly income? (Tick response)

- <R500.00
- R500.00 – R999.00
- R1000.00 – R1499.00
- R1500.00 – R1999.00
- R2000.00 – R2499.00
- R2500.00 – R2999.00
- ≥R3000.00

25. Do you have any dependents? (Tick response)

- Spouse
- 1 Child
- 2 Children
- 3 or more children
- None
- Other dependents (Specify ……)

26. Is your partner aware of your HIV status? (Tick response)

- Yes
- No
- Don't know

27. How many sexual partners have you had in the last 6 months?

- None
- 1
- 2
- 3 or more

**If your response is one or more partners** in the last 6 months, have you used a condom? (Tick response)

(a) Yes

(b) No

(c) Sometimes

28. Are you or (is your wife/girlfriend) pregnant? (Tick response)

- Yes
- No

29. Are you currently on contraception? (Tick response)

- Yes
- No

**If YES,** state type of contraception (Tick response)

(a) Injection

(b) Pill

(c) Condoms

(d) Loop

(e) Other (Specify ……..)

30. If you have child aged 5 years or less, what is the HIV status of the child? (Tick response)

- HIV +VE
- HIV -VE
- Don't know

31. What is your sexual orientation? (Tick response)

- Homosexual
- Heterosexual
- Bisexual
- Unknown

32. Any other relevant information of the patient?

## *Part 2: Baseline tests / investigations*

| | |
|---|---|
| 33. Measured Height | |
| 34. Measured Weight | |
| 35. Multipuncture Test Result (Multitest® CMI)<br>Date test administered<br>Date test result read<br>(a) 1 = Tetanus antigen<br>(b) 2 = Diphtheria<br>(c) 3 = Streptococcus C antigen<br>(d) 4 = Tuberculin antigen<br>(e) 5 = Glycerine (Control)<br>(f) 6 = Candida albicans (antigen)<br>(g) 7 = Trichophyton mentagrophytes antigen<br>(h) 8 = Proteus mirabilis antigen | |
| 36. Baseline TB Tests Results<br>(a) Sputum Smear Microscopy<br>(b) Sputum Culture<br>(c) Chest Radiography | |
| 37. Baseline Cytometer Readings<br>(a) CD4 Count<br>(b) CD8 Count<br>(c) CD4: CD8 Ratio<br>(d) TLC<br>(e) Other Test/s (Specify …….) | |
| 38. WHO Clinical Stage | |
| 39. Name of TB Lay Supervisor<br>➢ Address<br>➢ Telephone | |
| 40. Designated Area of TB Lay Supervisor & 'Relation' of TB Lay Supervisor to Patient | |

| | |
|---|---|
| 41. Karnofsky Performance Scale Score (Circle appropriate score)<br>(100) Normal, no complaints, no evidence of disease<br>(90) Able to carry on normal activity: minor symptoms of disease<br>(80) Normal activity with effort: some symptoms of disease<br>(70) Cares for self, unable to carry on normal activity or active work<br>(60) Requires occasional assistance but is unable to care for needs<br>(50) Requires considerable assistance and frequent medical care<br>(40) Disabled: requires special care and assistance<br>(30) Severely disabled: hospitalization is indicated, death imminent<br>(20) Very sick, hospitalization necessary: active treatment necessary<br>(10) Moribund, fatal processes progressing rapidly | |
| 42. Have you had persistent cough for more than 2 weeks?<br>➢ Yes<br>➢ No<br>(b) **If YES,** did your sputum contain blood (Tick response)<br>➢ Yes<br>➢ No | |
| 43. Have you had drenching night sweats in the last month? (Tick Response)<br>➢ Yes<br>➢ No | |
| 44. Have you had fever in the past month? (Tick Response)<br>➢ Yes<br>➢ No<br>➢ Not sure/Cant recall<br>**If YES,** was the fever<br>(a) intermittent<br>(b) Constant | |

| | |
|---|---|
| 45. Measured temperature of to Patient | |

| | |
|---|---|
| 46. Have you had chronic diarrhea for month or more? (Tick Response)<br>➢ Yes<br>➢ No | |

## *Part 3: Monthly screening/monitoring of patient clinic visits*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Name of Clinic | | | | Study ID Number | | | | |
| 47. Surname | | | | First name | | | | |
| 48. Date of Clinic Visit | Day | | Date | | Month | | Year | |
| 49. Type of Clinic Visit: | | | | | | | | |
| 50. Clinic Visit Number | | | | | | | | |

| 51. Potential Side effects to drug (Circle response) | |
|---|---|
| ➢ New skin rash | Yes/No |
| ➢ Itchiness | Yes/No |
| ➢ Pins & Needles | Yes/No |
| ➢ Numbness of the limbs | Yes/No |
| ➢ Nausea | Yes/No |
| ➢ Other (Specify ……..) | |

52. Have you had persistent cough for more than 2 weeks?

➢ Yes

➢ No

**If YES,** did your sputum contain blood (Tick response)

➢ Yes

➢ No

53. Have you had drenching night sweats in the last month? (Tick Response)

➢ Yes

➢ No

54. Have you had fever in the last month? (Tick Response)

➢ Yes

➢ No

➢ Not sure/Cant recall

**If YES,** was the fever

(a) intermittent

(b) Constant

| 55. Measured temperature of to Patient | |
|---|---|

| | |
|---|---|
| 56. Have you had chronic diarrhea in the last month? (Tick Response)<br>➢ Yes<br>➢ No | |
| 57. In the past month have you been to visit the any other outpatients clinic/hospital or private doctor? (Tick Response)<br>➢ Yes<br>➢ No<br>**If YES,** which outpatient clinic/hospital/doctor attended to you? | |
| 58. Urine Dipstick<br>(a) Billirubin<br>(b) Other (Specify …….) | |
| 59. Previous month's weight | |
| 60. This months weight difference | |
| 61. % Weight difference | |
| 62. Urine Dipstick<br>(a) Billirubin<br>(b) Other (Specify …….) | |
| 63. Previous month's weight | |
| 64. This months weight difference | |
| 65. % Weight difference | |
| 66. Is the Patient 'TB Suspect' (Yes ≥ 2 Symptoms: cough, sweats, fever, temperature and weight loss 2.5% within a month)<br>➢ Yes<br>➢ No<br>➢ Not sure | |
| 67. Urine Dipstick<br>(a) Billirubin<br>(b) Other (Specify …….) | |
| 68. Was the clinic visiting card allocated to you at the beginning of this trial/study study shown to the attending doctor/nurse? (Tick Response)<br>➢ Yes<br>➢ No<br>➢ Can't recall | |

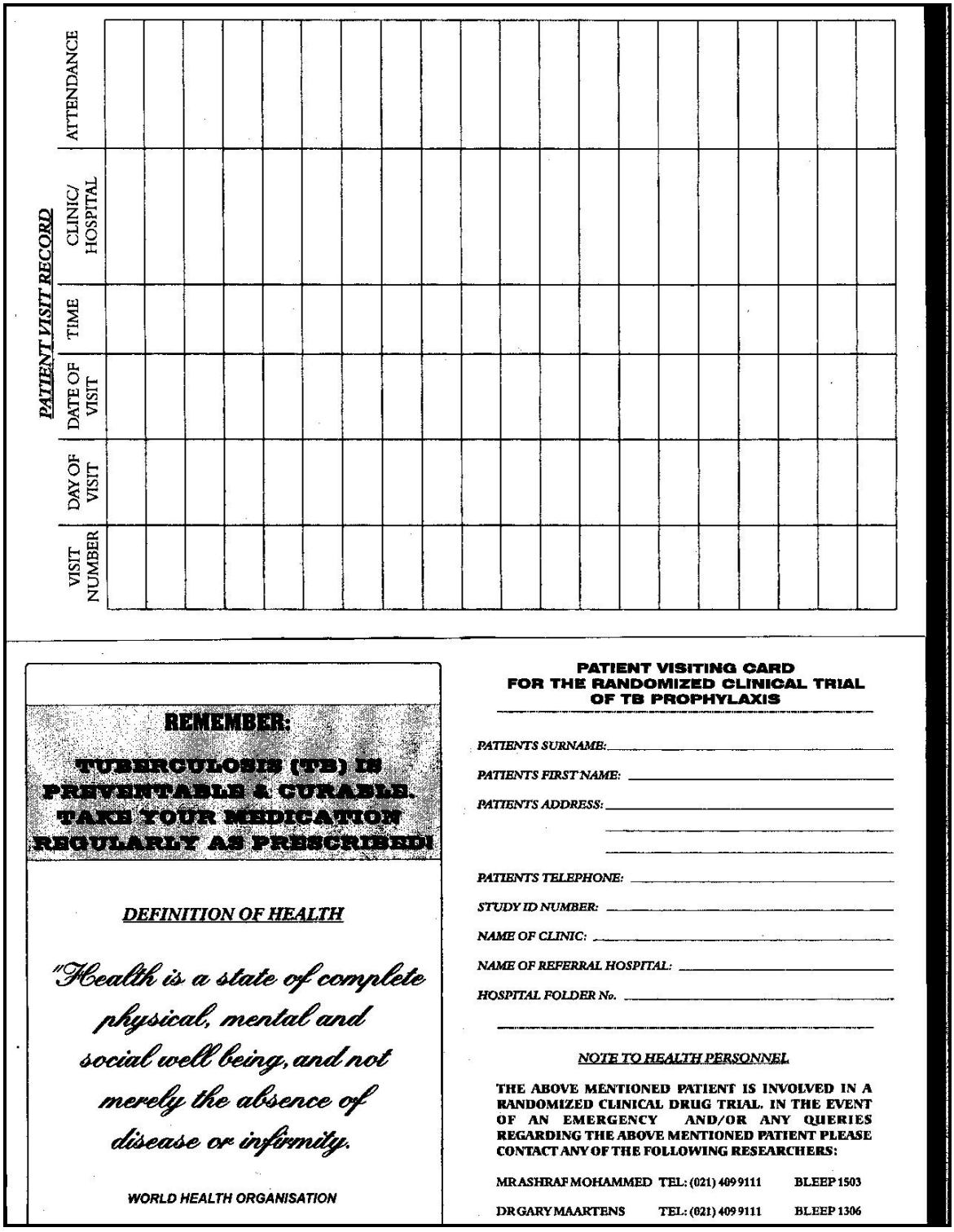
| | |
|---|---|
| 69. Urine Dipstick<br>(a) Billirubin<br>(b) Other (Specify …….) | |
| 70. Previous month's weight | |
| 71. This months weight difference | |
| 72. % Weight difference | |
| 73. Is the Patient 'TB Suspect' (Yes ≥ 2 Symptoms: cough, sweats, fever, temperature and weight loss 2.5% within a month)<br>➢ Yes<br>➢ No<br>➢ Not sure | |
| 74. Any other relevant notes on the Patient? | |
| 75. The number of Cotrimoxazole administered to the patient for the forthcoming 4 weeks (should always be 28 tablets. One tablet to be taken daily unsupervised by the patient. | Number of Cotrimoxazole tablets returned by patient = |
| 76. The number of Pyridoxine (Vitamin B6) administered to the patient for the forthcoming 4 weeks (should always be 8 tablets. One tablet to be taken twice weekly with INH/Placebo under the supervision of 'TB Lay Supervisor' | Number of Pyridoxine tablets returned by the patient = |
| 77. The number of INH/Placebo administered to the patient for the forthcoming 4 weeks (should always be 30 tablets and was under the supervision of the 'TB Lay Supervisor' on a twice weekly basis. The dosage for patients<br>➢ < 55kg was 4.5 tablets twice weekly<br>➢ ≥ 55kg was 5 tablets twice weekly | Number of INH/Placebo tablets returned by the patient = |
| 78. Patient's next monthly clinic visit?<br>➢ Date:<br>➢ Day<br>➢ Month<br>➢ Year | |

## *Part 4: TB tests & cytometer readings at 6-monthly intervals*

| **TB Tests & Cytometer Readings** | **6 Months** | **12 Months** | **18 Months** | **24 Months** |
|---|---|---|---|---|
| 79. Six monthly TB Tests Results<br>(a) Sputum Smear Microscopy<br>(b) Sputum Culture<br>(c) Chest Radiography | | | | |
| 80. Six monthly Cytometer Readings<br>(a) CD4 Count<br>(b) CD8 Count<br>(c) CD4: CD8 Ratio<br>(d) TLC | | | | |

# Appendix 3

## *Patient clinic visit card*



PATIENT VISIT RECORD

| VISIT NUMBER | DAY OF VISIT | DATE OF VISIT | TIME | CLINIC/ HOSPITAL | ATTENDANCE |
|---|---|---|---|---|---|
| | | | | | |

**REMEMBER:**

**TUBERCULOSIS (TB) IS PREVENTABLE & CURABLE. TAKE YOUR MEDICATION REGULARLY AS PRESCRIBED!**

***DEFINITION OF HEALTH***

*"Health is a state of complete physical, mental and social well being, and not merely the absence of disease or infirmity.*

*WORLD HEALTH ORGANISATION*

**PATIENT VISITING CARD FOR THE RANDOMIZED CLINICAL TRIAL OF TB PROPHYLAXIS**

*PATIENTS SURNAME:* _____

*PATIENTS FIRST NAME:* _____

*PATIENTS ADDRESS:* _____

_____

_____

*PATIENTS TELEPHONE:* _____

*STUDY ID NUMBER:* _____

*NAME OF CLINIC:* _____

*NAME OF REFERRAL HOSPITAL:* _____

*HOSPITAL FOLDER No.* _____

_____

***NOTE TO HEALTH PERSONNEL***

**THE ABOVE MENTIONED PATIENT IS INVOLVED IN A RANDOMIZED CLINICAL DRUG TRIAL. IN THE EVENT OF AN EMERGENCY AND/OR ANY QUERIES REGARDING THE ABOVE MENTIONED PATIENT PLEASE CONTACT ANY OF THE FOLLOWING RESEARCHERS:**

MR ASHRAF MOHAMMED TEL: (021) 409 9111 BLEEP 1503

DR GARY MAARTENS TEL: (021) 409 9111 BLEEP 1306

## Appendix 4

***Monthly supervisor tick sheet of participant:'TB lay supervisors' monthly report of TB preventive supervised therapy***

| | | | |
|---|---|---|---|
| Month | | Year | |
| Area/Location of TB Lay Supervisor | | | |
| Name of TB Lay Supervisor | | | |
| 'Relation' of TB Lay Supervisor to Patient | | | |

The tablets attached to this note are for the patient listed below. Please make sure that this patient takes the tablets regularly as prescribed.

The patient should take:

1. Trial Tablet (INCH/Placebo: TB Drug): ……. tablets 2 times a week
2. Vitamin Tablet (Pyridoxine):**1** tablet 2 times a week
3. Please record and advise clinic/researcher of any side effects or advise patient to report to clinic
4. Please return all unused tablets with patient at monthly clinic visit
5. With the unused tablets, please
6. Complete this form with a tick and initial corresponding to date to the tablets taken by patient
7. Hand completed form to the patient, to be submitted at the next clinic visit as a record of patient's monthly intake of trial medication (tablets),
8. You may comment on the patient's general health or any other general information you may wish to inform us regarding this patient on the back of this form.

| | | | | | |
|---|---|---|---|---|---|
| Patient's surname | | | | | |
| Patient's first name | | | | | |
| Patient's folder number | | | | | |
| Patient's medication number | | | | | |
| Week | Day | Date | TB Drug (INCH/Placebo) | Vitamin (Pyridoxine) | Initial |
| 1 | Monday | | | | |
| | Thursday | | | | |
| 2 | Monday | | | | |
| | Thursday | | | | |
| 3 | Monday | | | | |
| | Thursday | | | | |
| 4 | Monday | | | | |
| | Thursday | | | | |
| | | | | | |
| | | | | | |

# Appendix 5

## *Ethics and research committee approval*

**Faculty of Medicine**

Observatory 7925
Tel: (021) 406-6911
Fax No: (021) 47-8955
E-Mail address: MEDFAC@MEDICINE.UCT.AC.ZA

31 December 1996

ERC REF NO:248/96

Dr G Maartens
Dept of Medicine

Dear Dr Maartens

PREVENTING TUBERCULOSIS IN HIV-INFECTED ADULTS

I have pleasure in informing you that formal approval for the above study was granted by the Research Ethics Committee on the 31 December 1996.

Included is a list of Research Ethics Committee Members who have formally aporoved your protocol.

Yours sincerely

Prof. JP de V van Niekerk
Dean: Faculty of Medicine

rec96

## Appendix 6

### *Karnofsky performance status scale definition rating criteria*

| | | |
|---|---|---|
| KP Score ≥ 80 indicates the ability to carry on normal activities and to work with no special care needed | 100 | Normal, no complaints, no evidence of disease |
| | 90 | Able to carry on normal activity: minor symptoms of disease |
| | 80 | Normal activity with effort: some symptoms of disease |
| KP Score between ≥ 50 and 70 indicates the inability to work but able to live at home and care for most personal needs with varying amount of assistance needed | 70 | Cares for self, unable to carry on normal activity or active work |
| | 60 | Requires occasional assistance but is unable to care for needs |
| | 50 | Requires considerable assistance and frequent medical care |
| KP score of < 50 indicates the inability to care for oneself and requires equivalent of institutional or hospital care and where the disease may be progressing rapidly | 40 | Disabled: requires special care and assistance |
| | 30 | Severely disabled: hospitalization is indicated, death imminent |
| | 20 | Very sick, hospitalization necessary: active treatment necessary |
| | 10 | Moribund, fatal processes progressing rapidly |
| | 0 | Dead |